THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2025.34682
Med Bull Sisli Etfal Hosp 2025;59(3):338-344

Original Research

Does Co-Infection with HPV 16 Have a Worse Effect on Cervical Pathology than HPV 16 Alone?

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Abstract

Objectives: The aim of this study is to evaluate whether the presence of other HPV genotypes in addition to HPV16 infection has a negative effect on pathological outcomes.

Methods: This retrospective study was conducted using data from patients followed up at the Gynaecological Oncology Clinic of Antalya Training and Research Hospital between 2017 and 2025. Patients who were HPV16-positive and also carried other genotypes in addition to HPV16 were included in the study. HPV genotyping was performed using the Hybrid Capture 2 and CLART Genomica systems.

Results: Of the total 2,700 HPV (Human Papillomavirus) -positive women, 524 were HPV16-positive only, while 358 were positive for HPV16 along with other genotypes. Histopathological results, including CIN 2/3, HSIL, and invasive cancer, did not show significant differences between the two groups (p>0.05). However, abnormal colposcopy findings were statistically more prevalent in the co-infection group (p=0.037). Cigarette smoking was associated with a 1.27-fold increased risk for co-infection (p=0.026).

Conclusion: The findings of this study indicate that HPV16 is the primary determinant in the development of high-grade cervical pathology, and the presence of other high-risk HPV types does not significantly worsen histopathological outcomes. The results support the importance of a risk-based approach in cervical cancer screening processes and emphasize the need to prioritise early diagnosis and preventive interventions in HPV16-positive individuals.

Keywords: Coinfection, HPV-16, papillomavirus infections, uterine cervical neoplasms

Please cite this article as "Alci A, Yalcin N, Gokkaya M, Ekin Sari G, HR Turkmenoglu, Ureyen I, et al. Does Co-Infection with HPV 16 Have a Worse Effect on Cervical Pathology than HPV 16 Alone? Med Bull Sisli Etfal Hosp 2025;59(3):338-344".

Annually, more than 660,000 women globally receive a diagnosis of cervical cancer, and more than 348,000 perish from the disease.[1] The prevalence of concurrent multiple high-risk HPV (Human Papillomavirus] infections has been observed to be between 20% and 50% among patients exhibiting abnormal cervical cytology or histological findings.[2] The effect of HPV16 co-infection with other HPV types has been shown to include potential interaction with viral entry/replication, but also the ability of multiple high risk HPV types to sustain tissue oncogenic transformation in separate lesions or tissue sections.[3, 4] Recent studies have demonstrated that the transfection of other high risk HPV types into keratinocytes already infected with HPV16 can result in the suppression of HPV16 genome replication and a potential reduction in infectivity.[5] The process known as 'superinfection exclusion' is a viral mechanism that prevents a cell infected with

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Submitted Date: July 02, 2025 **Accepted Date:** August 18, 2025 **Available Online Date:** October 13, 2025

one virus from becoming infected with the same or a different virus. This phenomenon has been observed in HPV16 and HPV18 co-infections, and in vitro experiments suggest that HPV16 may inhibit HPV18 infection during the early stages of infection; however, this mechanism is ineffective in persistent cell lines. It has been hypothesised that both genomes compete for transcription during the early phases of infection, yet demonstrate equivalent replication efficiency in the persistent phase. This finding demonstrates that, in the initial phases of an infection, both genomes engage in a competitive process for transcription. However, in the context of persistent infections, these genomes exhibit equivalent replication efficacy.[6] Contemporary research underscores the notion that the isolated presence of HPV16 remains the most decisive prognostic determinant in the progression of cervical lesions. In contrast, concomitant infections with additional high-risk HPV types generally do not appear to exacerbate the risk of disease advancement.[7] On the contrary, certain combinations may even exert a modulatory effect, potentially stabilizing lesions at earlier histopathological stages. Nonetheless, particular scenarios merit caution: co-infections involving other potent oncogenic HPV types or occurring in immunocompromised individuals may act as surrogate indicators of persistent infection and, consequently, carry an elevated risk for neoplastic transformation.[8]

HPV types 16 and 18 are among the types with the highest oncogenic potential for cervical cancer and are generally analysed independently of each other in ASCCP guidelines. However, the primary objective of this study is to isolate and characterise the specific pathogenic effect of HPV16 in cervical lesions and to determine whether co-infections with high-risk or other HPV types detected are alongside HPV16 in the general population, compared to HPV16 infection alone. Furthermore, the data obtained will be evaluated in comparison with existing literature, and the findings will be interpreted from clinical and epidemiological perspectives.

Methods

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Antalya Training and Research Hospital (approval no: No: 16/10 / dated 24.10.2024). This retrospective study was conducted using data from patients who presented to the Gynecological Oncology Clinic at Antalya Training and Research Hospital between 2017 and 2025. Inclusion criteria comprised women who tested positive for HPV type 16 alone or in combination with other HPV types. Patients were excluded if they were positive for HPV types other than HPV 16, had undergone hysterectomy, or had a confirmed diagnosis of any gynecological malignancy. HPV screening was performed using the Hybrid Capture 2 assay (Qiagen), a validated and widely utilized diagnostic method in clinical practice. For samples testing positive for HPV, further genotyping was carried out using the CLART HPV kit (Genomica) to determine specific viral subtypes. Relevant clinical and demographic data were extracted from electronic medical records and the hospital's database system. Data included patient age, menopausal status, and histopathological findings from colposcopy-directed cervical biopsies and endocervical curettage (ECC). ECC was indicated in cases where the squamo-columnar junction (SCJ) was partially or completely unvisualized due to factors such as bleeding, inflammation, or cervical scarring. The ECC procedure was performed using a Novak curette to obtain samples from the entire endocervical canal, which were subsequently processed for histopathological examination. Histological outcomes from cervical biopsy and ECC specimens were classified into the following categories: normal cervical tissue, cervicitis, cervical intraepithelial neoplasia (CIN 1, CIN 2, CIN 3), high-grade squamous intraepithelial lesion (HSIL), suspected invasive carcinoma, microinvasive carcinoma, and invasive cervical cancer.

Statistical Analysis

Statistical analyses were performed using SPSS 27.0 software (IBM Inc, Chicago, IL, USA). Visual summarisations were performed with Graphpad prism 10.4.0 software. Kolmogrov-Smirnov test, histogram analyses, skewness/kurtosis data and Q-Q plots were used to evaluate the conformity of numerical variables to normal distribution. Qualitative parameters were defined as frequency (N) or percentage (%). Quantitative parameters were expressed as mean±standard deviation. In quantitative parameters with normal distribution, intergroup variance analyses were performed with Levene's test. Relationships between two independent groups were analysed by independent t-test. Associations between categorical parameters were analysed using Pearson's chi-square analysis or Fisher's exact test. Binary outcomes and associated parameters were analysed using (LR) analyses. Cut-off values of quantitative parameters were determined by ROC analyses. Distributions between categorical parameters were summarised with heat maps. The analyses were performed with a 95% confidence interval, and a type-I error rate of 5% ($\alpha=0.05$) was taken as a basis and $p<0.05$ was accepted as the significant limit.

Results

During the study period, 2,700 patients were admitted to the gynaecological oncology clinic with HPV positivity. The study population consisted of 524 patients (59.4%) with HPV 16 positivity, 56 patients (6.3%) with HPV 16+18 positivity, 281 patients (31.9%) with HPV 16 and other positivity, and 21 patients (2.4%) with HPV 16+18 and other positivity. In the study cohort, a to-

Table 1. Summary of the general distribution of smoking, menopause and HPV status

Feature	Frequency (N)	Percentage (%)	
Cigarette			
Nonsmoker	365	41.4	
Smoker	439	49.8	
Unknown	78	8.8	
Menopausal status			
Unknown	10	1.1	
Premenopausal	620	70.3	
Postmenopausal	252	28.6	
HPV status			
Group 1 (59.4%)			
HPV 16 (Group 1)	524	59.4	
HPV16 + 18	56	6.3	
Group 2 (40.6%)			
HPV 16 and other	281	31.9	
HPV 16+18 and other	21	2.4	
	Min	**Max**	**Mean±SD**
Age	21	68	43.7±9.1

tal of 439 patients (49.8%) were classified as smokers, while 365 patients (41.4%) were classified as non-smokers (Table 1). The smoking status of 78 patients (8.8%) remained uncertain. The mean age of the study cohort was 43.7 years (±9.1 years), and a summary of the age distribution is given in Figure 1.

The number of postmenopausal patients was 252 (28.6%), while the number of premenopausal patients was 620 (70.3%) (Table 1).

The general distribution of diagnostic approaches is summarised in Table 2. The heat map of the distribution of

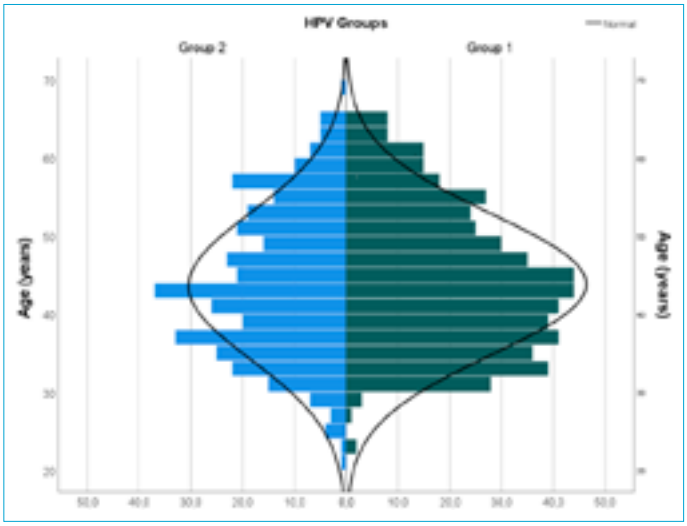

Figure 1. Group 1 and 2 age distribution summary.

Table2. General distribution of diagnostic approaches.

Diagnostic Approach	Frequency (N)	Percentage (%)
Cytology		
NILM	283	32.1
Infection	138	15.6
Inadequate	109	12.4
ASCUS	65	7.4
LSIL	74	8.4
ASC-H	13	1.5
HSIL	10	1.1
AGC	3	0.3
Invasive suspicion	0	0.0
Endometrial degenerated cells	0	0.0
Unknown	186	21.1
AIS	1	0.1
Colposcopy		
Normal	281	31.9
Abnormal	588	66.7
Inadequate	13	1.5
Did you get a pathology?		
No	1	0.1
Yes	881	99.9
Cervical biopsy		
Not done	275	31.2
Cervix tissue	90	10.2
Servisit	145	16.4
SEN	13	1.5
CIN	5	0.6
CIN 1	169	19.2
CIN 2	60	6.8
CIN 3	107	12.1
Suspicion of invasive Ca/microinvasive	5	0.6
Invasive Ca	8	0.9
HSIL	5	0.6
ECC		
Not done	141	16.0
Negative	622	70.5
SEN	6	0.7
CIN	3	0.3
CIN1	28	3.2
CIN2	21	2.4
CIN3	51	5.8
Suspicion of invasive CA	2	0.2
Invasive CA	3	0.3
HSIL	5	0.6
Pathology result		
Cervix tissue	325	36.8
Servisit	135	15.3
CIN 1	209	23.7
CIN2 - CIN3 - HSIL	194	22.0
Suspicion of invasive ca/microinvasive	6	0.7
İnvasive Ca	13	1.5

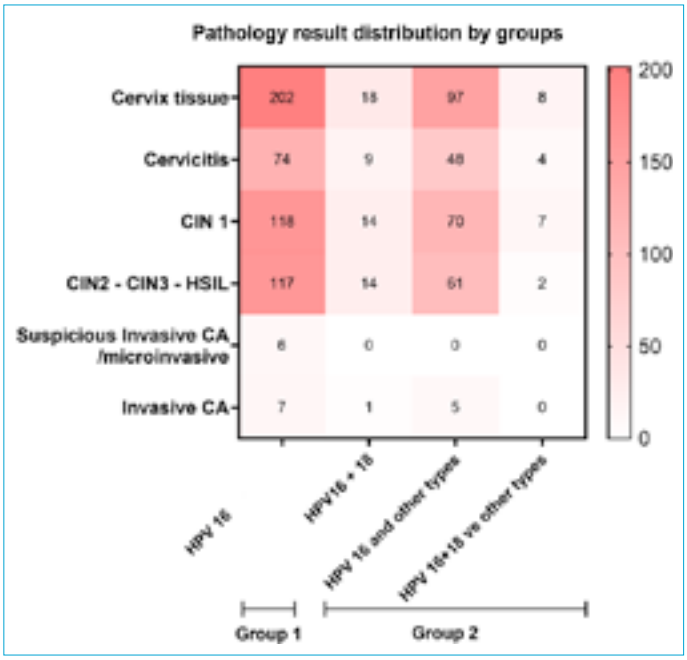

Figure 2. Heat map summary of pathology result distributions by groups according to frequency (p>0.05).

pathology results according to frequency revealed no significant difference between the groups in terms of cervical pathology results (p>0.05) (Fig. 2).

Subsequent analysis revealed that age, menopausal status and smoking did not demonstrate statistical differences between the groups (p=0.721, p=0.405, p=0.071) (Table 3).

However, a statistically significant difference was identified between the two groups with respect to cytological results (p=0.004). The study revealed that 342 cases (65.27%) in Group 1 and 246 cases (68.72%) in Group 2 exhibited ab-

Table 3. Comparison of the distribution of diagnostic approaches between groups

Diagnostic Approach	Group 1 (n=524, %59.4)	Group 2 (n=358, %40.6)	
	Distribution†		P
Age	43.7±9.0	43.5±9.4	0.721[a]
Cigarette			
Does not drink	233 (44.47)	132 (36.87)	0.071[b]
Drinking	249 (47.52)	190 (53.07)	
Unknown	42 (8.02)	36 (10.06)	
Menopausal status			
Unknown	8 (1.53)	2 (0.56)	0.405[b]
Premenopausal	368 (70.23)	252 (70.39)	
Postmenopausal	148 (28.24)	104 (29.05)	

†Data are expressed as mean±standard deviation or frequency (%) according to their distribution. [a]Independent t-test, [b]Pearson chi-square analysis.

Table 4. Comparison of the distribution of diagnostic approaches between groups

Diagnostic Approach	Group 1 (n=524, %59,4)	Group 2 (n=358, %40,6)	
	Frequency (%)		P
Cytology			
NILM §	149 (28.44)	134 (37.43)	0.004[a]
Infection	86 (16.41)	52 (14.53)	
Inadequate	56 (10.69)	53 (14.8)	
ASCUS	36 (6.87)	29 (8.1)	
LSIL §	52 (9.92)	22 (6.15)	
ASC-H	6 (1.15)	7 (1.96)	
HSIL	8 (1.53)	2 (0.56)	
AGC	2 (0.38)	1 (0.28)	
Invasive suspicion	0 (0)	0 (0)	
Endometrial degenerated cells	0 (0)	0 (0)	
Unknown §	128 (24.43)	58 (16.2)	
AIS	1 (0.19)	0 (0)	
Colposcopy			
Normal	178 (33.97)	103 (28.77)	0.037[b]
Abnormal	342 (65.27)	246 (68.72)	
Inadequate §	4 (0.76)	9 (2.51)	
Did you get a pathology?			
No	0 (0)	1 (0.28)	0.406[a]
Yes	524 (100)	357 (99.72)	
Cervical biopsy			
Not done	173 (33.02)	102 (28.49)	0.052[a]
Cervix tissue	54 (10.31)	36 (10.06)	
Servisit	84 (16.03)	61 (17.04)	
SEN	7 (1.34)	6 (1.68)	
CIN	5 (0.95)	0 (0)	
CIN 1	91 (17.37)	78 (21.79)	
CIN 2	27 (5.15)	33 (9.22)	
CIN 3	69 (13.17)	38 (10.61)	
Suspicion of invasive Ca/ microinvasive	5 (0.95)	0 (0)	
Invasive Ca	5 (0.95)	3 (0.84)	
HSIL	4 (0.76)	1 (0.28)	
ECC			
Not done	89 (16.98)	52 (14.53)	0.075[c]
Negative	357 (68.13)	265 (74.02)	
SEN	1 (0.19)	5 (1.4)	
CIN	1 (0.19)	2 (0.56)	
CIN1	19 (3.63)	9 (2.51)	
CIN2	14 (2.67)	7 (1.96)	
CIN3	36 (6.87)	15 (4.19)	
Suspicion of invasive CA	2 (0.38)	0 (0)	
invasive CA	3 (0.57)	0 (0)	
HSIL	2 (0.38)	3 (0.84)	

Table 4. Comparison of the distribution of diagnostic approaches between groups (Cont.)

Diagnostic Approach	Group 1 (n=524, %59,4)	Group 2 (n=358, %40,6)	
	Frequency (%)		P
Pathology result			
Cervix tissue	202 (38.55)	123 (34.36)	0.20[b]
Servisit	74 (14.12)	61 (17.04)	
CIN 1	118 (22.52)	91 (25.42)	
CIN2 - CIN3 - HSIL	117 (22.33)	77 (21.51)	
Suspicion of invasive Ca/ microinvasive	6 (1.15)	0 (0)	
Invasive Ca	7 (1.34)	6 (1.68)	

[§]=The subcategories that cause significance and proportional differences between the groups are marked. [a]Fisher's exact test; [b]Pearson chi-square analysis.

Table 5. Separate (univariate) investigation of the effect profiles and predictive properties of the parameters on co-infection (Group 2)

	Co-infection				
Factor	B	Nagelkerke R^2	p	OR	95%CI
Age (years)	-0.003	<0.001	0.224	0.72	0.983 - 1.012
Menopausal status	0.080	<0.001	0.583	1.08	0.815 - 1.440
Cigarette	0.243	0.008	0.026	1.27	1.030 - 1.579

Reference category: Group 1., LR: Likelihood Ratio; CI: Confidence Interval; OR=Odd ratio.

normal colposcopy results, indicating a statistically significant difference (p=0.037). However, cervical biopsy results were within the limit of statistical significance between the two groups (p=0.052) (Table 4).

Furthermore, smokers demonstrated a 1.27-fold elevated prevalence of co-infection (p=0.026, OR=1.27) (Table 5).

Notwithstanding the high prevalence of smoking observed among individuals with CIN2-CIN3, HSIL and invasive cancer, the most significant discrepancy was identified among those with invasive cancer. The observed variation in cervical tissue between these groups can be attributed to the substantial sample size of the study population (Fig. 3).

Discussion

The primary findings of our study indicated that there was no statistically significant difference between the cervical pathology results of patients with HPV 16 co-infection and individuals with HPV 16 infection only. In addition, the risk of co-infection increased 1.27-fold in patients who smoked,

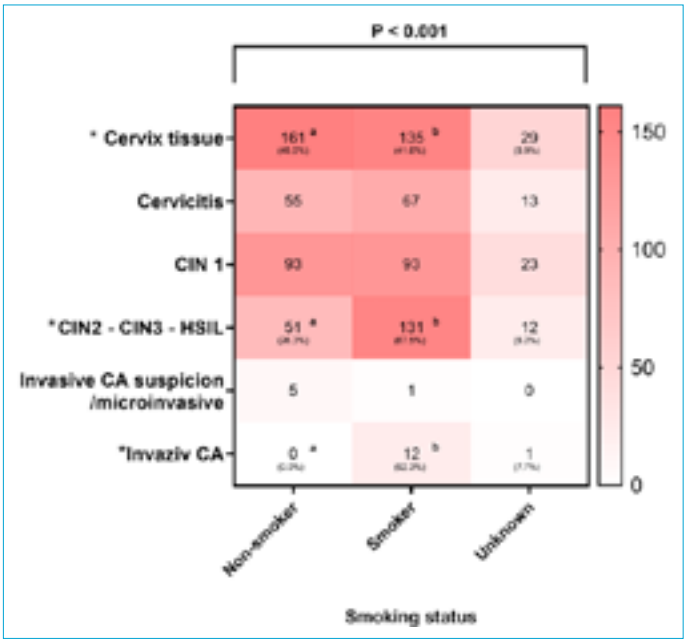

Figure 3. Visual summary of the distributional relationship between smoking and pathology and frequency values (Fisher's exact test; p<0.001) (*: Pathology subgroups that cause distributional differences are marked; (a, b): Data are divided into row percentages and those that differ in pairwise comparisons according to smoking status are marked). Cervical tissue, CIN2 - CIN3 - HSIL and invasive CA showed higher smoking rates, but the most significant difference was observed in those with invasive CA.

and it was observed that smoking rates were higher in patients diagnosed with CIN 2, CIN 3, HSIL and invasive cancer. The most significant difference was observed in patients diagnosed with invasive cancer.

In a study of 963 patients, a group infected only with HPV-16 (n=74) was compared with a group with HPV-16 positivity with high risk (n=68) and a group with HPV-16 co-infection with other types of HPV (n=27). The study found a relative risk [RR] of 1.39 with 95% confidence interval to be increased in the high risk HPV group. The discrepancy observed in our study may be attributable to numerical disparities between the groups.[9] In another study in the literature, analyses of the effect of HPV16 and HPV18 coinfection on CIN showed an odds ratio (OR) of 3.8 for this coinfection compared with HPV16 infection alone (95% CI: 2.5-5.7, p=0.004). A similar result was observed in the analysis of the association between HPV16 and HPV52 coinfection, yielding an odds ratio of 3.6 (95% CI: 2.6-5.1, p=0.009). Collectively, these findings suggest that coinfection with HPV18 and HPV52 is associated with a significantly higher risk of developing CIN (Cervical Intraepithelial Neoplasia) compared to HPV16 infection alone.[10] In contrast to the present study, the aforementioned study included all CIN lesions. In a subgroup analysis of a study conducted by Spi-

nillo et al.[10] to evaluate the clinical outcomes of co-infection with HPV 16 and other high-risk HPV types in women with a histological diagnosis of CIN or invasive cervical cancer, the odds of CIN3+ were higher in women with co-infection with HPV16 and HPV18 (OR=3.8, 95% CI 2.5-5.7, p=0.004, compared with HPV16 alone) or HPV52 co-infection (OR=3.6, 95% CI 2.6-5.1, p=0.009, compared with HPV infection alone) was higher than the odds ratio associated with single HPV infection. One of the study's findings was that multiple infections had no effect on residual disease [10]. The differences between the two studies appear reasonable given that the

diagnosis of HPV co-infection is strongly influenced by age, the type of genotyping system used, and the severity of cervical disease identified by biopsy or conisation.[11-13]

Wu et al.[14] demonstrated in a subgroup analysis of a population-based study that concurrent infection with HPV16 and other high-risk genotypes did not significantly increase the risk of CIN3+ lesions compared to HPV16 infection alone. (Odds ratio [OR]=0.637, 95% confidence interval [CI]=0.493–0.822). In the present study, HPV18 was not analysed as a separate subgroup. The primary motivation for this decision stemmed from the study's objective of isolating and characterising the specific pathogenic potential of HPV16 in cervical lesions. The analysis of HPV18 in isolation could have introduced confounding effects, which would have obscured the distinct clinical course attributable to HPV16. Furthermore, the prevalence of HPV18 infection either alone or in co-infection with HPV16 was extremely low in the present cohort, a finding that is analogous to the low rates reported in the population-based study by Wu et al.,[14] in which HPV16/18 co-infection was observed in only 1.13% of cases. This low frequency prevented the conduct of a statistically robust subgroup analysis for HPV18 within the current dataset. As a result, HPV18 was included in the general 'other high-risk HPV' category, allowing the analysis to continue focusing on determining whether co-infection alters the disease course defined by HPV16.The distribution of HPV types among the 4,933 patients who underwent colposcopy was as follows: 52.38% were infected with HPV16 alone. 23.54% were co-infected with HPV16 and at least one other high-risk HPV type. The proportion of individuals infected with both HPV16 and HPV18 was 1.13%, and co-infections involving these two types plus other high HPV types were also found at 1.13%. [14] In a subgroup analysis of a study involving 7,940 patients in China, compared to HPV 16 infection alone, the risk of CIN 3+ was significantly reduced in women infected with HPV 16 plus other high-risk HPV [OR=0.621, 95% CI=0.511–0.755], compared to HPV 16 + low-risk HPV (OR=0.620, 95% CI 0.436–0.883) and HPV 16 + low risk HPV + other hrHPV (OR=0.248, 95% CI 0.157–0.391), the risk of CIN 3+ was significantly reduced. In contrast to our study, the prevalence of CIN 3+ was associated with an increase in the severity of cytological abnormalities in HPV 16/18-positive women, peaking at cytology HSIL+ (89.9% and 82.3%), which represented a significantly higher risk compared to NILM (Negative for Intraepithelial Lesion or Malignancy) (OR=65.466, 95% CI 50.234–85.316). This difference may be attributed to the larger sample size of this study.[15] In conclusion, this study found that HPV16 co-infection, excluding HPV18, was associated with a lower or similar risk of high-grade cervical lesions compared to HPV16 alone.These findings suggest that the presence of multiple HPV types in HPV16-positive individuals may attenuate the pathogenic potential of the infection, possibly through mechanisms such as viral interference or cross-protective immune responses. Such interactions may contribute to a less aggressive clinical course in the context of co-infection.

One potential explanation for the discordant findings in the literature is based on molecular and immunological interactions between HPV genotypes. The extant literature has described a mechanism known as 'superinfection exclusion', which suggests that when a cell is already infected with one HPV, it may prevent the entry or replication of a second HPV type. This mechanism may provide a rationale for the observation of reduced pathological progression in certain co-infection scenarios.[6] Conversely, as demonstrated by Sobota et al.,[16] co-infection with HPV genotypes belonging to the same phylogenetic group may suppress the progression of viral oncogenesis due to competition for host cell resources.

When interpreting the results, it is important to consider the limitations of this study. First, the retrospective design of the study limits the establishment of cause-and-effect relationships. Second, the lack of long-term follow-up data prevents the dynamic assessment of the potential effects of concurrent infections on disease progression. Third, the biological significance of concurrent infections could not be thoroughly analysed since HPV viral load was not measured. Additionally, the immunological status of the patients was not included in the study, which may have affected the persistence or clearance of the infection in some cases. Finally, the fact that the study was conducted at a single centre may limit the generalisability of the findings to the general population. However, the study also has important strengths. The histopathological confirmation of cervical pathology and the examination of a well-defined patient group enhance the reliability of the clinical outcomes. The emphasis on the effects of HPV16 and co-infections provides important insights into their roles in disease progression. Additionally, the use of real-world data ensures that the findings are consistent with routine clinical

practice. The presence of these characteristics facilitates the development of risk-based screening and management strategies for individuals with HPV16-positive results.

In conclusion, the findings of our study emphasise the crucial role of HPV16 in the progression of clinically significant cervical pathology. In the context of co-infections with other HPV types, HPV16 remains the dominant determinant of disease severity. The absence of a significant effect of concurrent infections on histopathological outcomes suggests that the presence and persistence of HPV16 should be given greater consideration in routine clinical decision-making. The findings support the prioritisation of early diagnosis and preventive strategies for individuals testing positive for HPV16, thereby improving patient risk classification and guiding more targeted clinical management.

Disclosures

Ethics Committee Approval: The study was approved by Antalya Training and Research Hospital Clinical Research Ethics Committee (No: 6/25, dated 09.05.2024).

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared that they have no conflict of interest.

Funding: There was no external funding about this manuscript.

Authorship Contributions: Concept – A.A.; Design – N.Y., M.G.; Supervision – M.G., A.A.; Fundings – G.E.S., H.R.T.; Materials – H.R.T.; Data collection &/or processing – I.U.; Analysis and/or interpretation – T.T., A.A.; Literature search – N.Y.; Writing – I.U.; Critical review – A.A.

Use of AI for Writing Assistance: The authors declared that artificial intelligence-supported products were not used in the production of the study.

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