

The impact of COVID-19 (SARS-CoV-2) vaccines on high-risk human papillomavirus clearance and cervical cytology in patients undergoing cervical excisional procedures

COVID-19 (SARS-CoV-2) aşılarının servikal eksizyonel işlem yapılan hastalarda yüksek riskli human papilloma virüsü temizliği ve servikal sitoloji üzerindeki etkisi

 Mustafa ŞAHİN¹,  Tufan ARSLANCA²

¹Gynecological Oncology Surgery Clinic, Konya City Hospital, Konya, Türkiye

²Gynecological Oncology Surgery Clinic, Ankara Bilkent City Hospital, Ankara, Türkiye

ABSTRACT

Aim: This study aims to investigate the effects of COVID-19 (SARS-CoV-2) vaccines on high-risk Human Papillomavirus (hr-HPV) clearance and cervical cytology results in patients undergoing cervical excisional procedures.

Materials and Methods: A total of 686 patients were analyzed in the Gynecological Oncology Surgery Clinic between October 2020 and July 2022. Among these, 350 patients had not received the COVID-19 vaccine, and 336 had received it. Cervical cytology and hr-HPV DNA analysis were performed on the patients 6 months after the cervical excisional procedure. Clinical data, including patients' vaccination status, were obtained from the national electronic medical record database, patient files, and face-to-face inquiries.

Results: There was no significant difference between the vaccinated and unvaccinated groups in terms of age, parity, smoking, oral contraceptive use, cervical cytology, hr-HPV DNA status, cervical biopsy, endocervical curettage, type of excisional procedure, results of excisional procedure and endocervical curettage, and surgical margin status ($p>0.05$ for all comparisons). No significant difference was observed in the cervical cytology results 6 months post-procedure between the vaccinated and unvaccinated groups ($p=0.566$, 95% CI=1.130-1.549). Similarly, no significant difference was found in hr-HPV DNA clearance between the two groups 6 months post-procedure ($p=0.217$, 95% CI=1.412-1.750).

Conclusion: The systemic effects of COVID-19 vaccines are not fully understood. Our study is among the few that investigate the impact of COVID-19 vaccines on hr-HPV DNA clearance and cervical cytology results. Current literature, similar to our findings, does not demonstrate a significant effect of COVID-19 vaccination on hr-HPV clearance and cervical cytology results. Given the strong immunogenic response elicited by COVID-19 vaccination, the potential impact of this non-specific systemic inflammatory response on hr-HPV DNA clearance warrants further investigation. This study found no difference in cervical cytology and hr-HPV DNA persistence between vaccinated and unvaccinated patients 6 months post-cervical excisional procedure. However, comprehensive studies are needed for better interpretation and acceptance of these findings.

Keywords: COVID-19 (SARS-CoV-2) vaccines, cervical excisional procedure, high-risk human papillomavirus clearance, cervical cytology

ÖZ

Amaç: Bu çalışmada servikal eksizyonel işlem uygulanan hastalarda Covid 19 (SARS-CoV-2) aşılarının yüksek riskli Human Papilloma Virüs klerensine ve servikal sitoloji sonuçlarına etkilerini araştırmayı amaçlıyoruz.

Gereçler ve Yöntem: Ekim 2020 ile Temmuz 2022 tarihleri arasında Jinekolojik onkoloji cerrahisi kliniğinde Covid 19 aşısı olmamış 350 hasta ve Covid 19 aşısı olmuş 336 hasta olmak üzere toplam 686 hasta analiz edildi. Hastaların servikal eksizyonel işlemden 6 ay sonraki servikal sitoloji ve hr-HPV DNA analizi yapıldı. Hastaların aşı durumu da dahil olmak üzere klinik veriler, ulusal elektronik tıbbi kayıt veri tabanından, hasta dosyalarından ve hastanın kendisinden yüz yüze sorularak elde edildi.

Bulgular: İki grup arasında yaş, parite, sigara, oral kontraseptif kullanımı, servikal sitoloji, hr-HPV DNA durumu, servikal biopsi ve endoservikal küretaj, eksizyonel işlem tipi, eksizyonel işlem ve endoservikal küretaj sonucu, cerrahi sınır durumu, açısından fark yoktu (sırasıyla $p=0,588$, $p=0,464$, $p=0,319$, $p=0,315$, $p=0,428$, $p=0,655$, $p=0,302$, $p=0,610$, $p=0,734$, $p=0,237$, $p=0,198$, $p=0,594$). Aşılanmayan ve aşılanan gruplarda 6 ay sonrası servikal sitoloji sonuçlarında anlamlı fark yoktu ($p=0,566$, %95 CI=1,130-1,549). Aşılanmayan ve aşılanan gruplarda 6 ay sonrası hr-HPV DNA açısından anlamlı fark yoktu ($p=0,217$, %95 CI=1,412-1,750).

Tartışma: Covid 19 aşılarının neden olduğu sistemik etkileri günümüzde tam olarak aydınlatılamamıştır. Çalışmamız Covid 19 aşılarının hr-HPV DNA klerensine ve servikal sitoloji sonuçlarına olan etkisini araştıran literatürdeki yapılmış sayılı çalışmadan biridir. Yapılmış güncel çalışmalarda çalışmamızda elde ettiğimiz sonuçlara benzer şekilde Covid 19 aşılamaının hr-HPV klerensinde ve servikal sitoloji sonuçları üzerinde etkisi gösterilemedi. Covid 19 aşılamaının güçlü bir immünojenik reaksiyon ortaya çıkardığı göz önüne alındığında, bu spesifik olmayan sistemik inflamatuvar yanıtın, hr-HPV DNA klerensine olası etkisi merak konusudur.

Sonuç: Çalışmamızda Covid 19 için aşılanmayan ve aşılanan hastaların servikal eksizyonel işlemden 6 ay sonrasındaki servikal sitoloji ve hr-HPV DNA persistans sonuçları arasında fark saptanmadı. Ancak elde edilen sonuçların daha iyi yorumlanıp kabul görmesi için kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Covid 19 (SARS-CoV-2) aşıları, servikal eksizyonel işlem, yüksek riskli human papilloma virüs klerensi, servikal sitoloji

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Sorumlu Yazar/Corresponding Author: Mustafa ŞAHİN, Akabe Mahallesi, Adana Çevre Yolu Caddesi. No:135/1, 42020 Karatay-Konya, Türkiye

E-mail: mustafasahin1163@gmail.com

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INTRODUCTION

Human papilloma virus (HPV) is an oncogenic DNA virus with a central role in the development of cervical cancer. The presence of HPV alone is not sufficient for the development of a pre-invasive cervical lesion and HPV persistence plays a critical role (1). Persistent infection with Human Papilloma Virus (HPV) is the primary cause of nearly all preinvasive cervical lesions and cervical cancer. There are over 200 different types of HPV, including high-risk (hr) HPV subtypes. Few HPV subtypes have carcinogenic potential. The high-risk HPV types (HR-HPV) are 18, 31, 33, 35, 39, 45, 51, 56, 58, 59, 68, 73 and 82, especially 16 (2). Of these, HPV 16 and HPV 18 are the types most associated with invasive cancers and cause 65-75% of cases (3). While most HPV infections are typically cleared by the immune system within an average of 6-18 months, approximately 10% of cases persist in women, leading to cervical intraepithelial neoplasia (CIN) in 20-30% of cases and cervical cancer in 1-2% of cases (1).

CIN is a preinvasive condition that precedes cervical cancer and is equivalent to the term cervical dysplasia. Cervical lesions with mitoses and immature cells limited to the lower third of the epithelium are typically referred to as CIN 1, and involvement of the middle and upper thirds are referred to as CIN 2 and CIN 3, respectively. In contrast, for patients with CIN 2 and 3 lesions, the recommended strategy is excision, intended to stop progress toward carcinoma, followed by intensified surveillance. The main treatment methods for preinvasive cervical lesions include excisional procedures such as Loop Electrosurgical Excision Procedure (LEEP) or conization. Studies have shown a residual disease rate of 5-20% following excisional procedures (2).

COVID-19, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is an infectious disease affecting the respiratory tract. Lymphocytopenia observed during infection potentially involves CD4+ and some CD8+ T cells. This impairs the innate and acquired immune responses, delaying the clearance of the virus and causing an overactive neutrophil and macrophage response (3).

Various vaccines are available for COVID-19 in our country. The Pfizer/BioNTech mRNA vaccine induces an immune response by injecting the genetic code of the virus's Spike protein (S-protein) encapsulated in lipid nanoparticles into the human body. The CoronaVac (Sinovac) vaccine is an inactivated vaccine developed by growing and inactivating the live SARS-CoV-2 virus in the laboratory.

A study on the effectiveness of COVID-19 vaccines and the waning of immunity over time showed that 8 months after the administration

of two doses of COVID-19 vaccine, immune function was lower in vaccinated individuals than in unvaccinated individuals (1).

The systemic effects caused by Covid 19 vaccines have not been fully elucidated to date. Inflammatory processes play an active role in the persistent development of HPV infections. Considering that Covid 19 vaccination elicits a strong immunogenic reaction, the possible effect of this nonspecific systemic inflammatory response on HPV persistence is a matter of curiosity.

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In our study, we investigated the effects of COVID-19 vaccines on HR-HPV clearance and cervical cytology.

MATERIALS AND METHODS

Ethical approval for the study was obtained from the Ethics Committee of Necmettin Erbakan University (Decision No: 5439, dated 10.01.2025). All patients signed informed consent forms allowing the use of their clinical data. The study protocol complies with the ethical principles of the 1975 Declaration of Helsinki.

Between October 2020 and July 2022, 686 patients over 24 years of age with high-risk cervical preinvasive lesions and hr-HPV DNA positivity who underwent cervical excisional procedures at Konya City Hospital Gynecological Oncology Surgery Clinic were analyzed. Patients who received the COVID-19 vaccine 3 months before or after the excisional procedure, with no additional medical problems or medication history that could impair immune response, were included. Patients with malignant or carcinoma in situ pathology reports, those requiring reconization, unvaccinated patients with additional medical problems or medication history that could impair immune response, were excluded from the study.

Cervical excisional procedures were performed by a surgical team specialized in gynecological oncology. Cytology and surgical samples were evaluated by specialized pathologists. Pathology and HPV DNA test results were assessed following the 2019 ASCCP guidelines (4). Conization was performed using a scalpel (cold conization) or needle-tip cautery, depending on the surgeon's

preference. HPV DNA analysis was performed using the Hybrid Capture 2 HPV DNA test (hc2; Qiagen, Hilden, Germany). The 6-month post-procedure HPV DNA and cervical cytology results were compared with the pre-procedure results. Patients who received at least one dose of Pfizer/BioNTech mRNA vaccine or Sinovac Life Sciences (inactivated) vaccine were included. Clinical data, including vaccination status, were obtained from the national electronic medical record database, patient files, and face-to-face inquiries.

Statistical Analysis

Statistical analysis was performed using SPSS version 22 (IBM, Chicago, USA). Descriptive data were presented as n (%) for categorical variables and mean±standard deviation (Mean±SD) for continuous variables. Chi-square and Fisher's Exact tests were used to evaluate differences between groups. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 786 patients were evaluated for eligibility. Fifty-three individuals were excluded for not meeting the inclusion criteria, leaving 733 patients with hr-HPV DNA infection, 372 of whom were unvaccinated and 361 vaccinated. During follow-up, 22 and 25 patients in the unvaccinated and vaccinated groups, respectively, were lost to follow-up or discontinued treatment. Ultimately, 350 unvaccinated and 336 vaccinated patients were analyzed. The patient selection flowchart is shown in Figure 1.

The mean age of the unvaccinated group (n=350) was 35.22±6.92 years, and the vaccinated group (n=336) was 33.65±5.48 years. The mean parity was 2.12±1.30 in the unvaccinated group and 1.91±1.04 in the vaccinated group. Smoking prevalence was 67.4% in the unvaccinated group and 61.6% in the vaccinated group. Oral contraceptive use was reported in 42.9% of unvaccinated patients and 39.2% of vaccinated patients. There was no significant difference between the unvaccinated and vaccinated groups in terms of age, parity, smoking, oral contraceptive use, cervical cytology, hr-HPV DNA status, cervical biopsy, endocervical curettage, type of excisional procedure, results of excisional procedure and endocervical curettage, and surgical margin status ($p>0.05$ for all comparisons). Demographic and clinicopathological data of the patients are summarized in Table 1.

There was no significant difference in cervical cytology results between the unvaccinated and vaccinated groups 6 months post-procedure, with benign cytology rates of 50.3% vs. 47.9%, ASCUS, LSIL rates of 28% vs. 29%, ASC-H, AGC, HSIL rates of 12.6% vs. 14.7%, and unknown rates of 9.1% vs. 4.1%, respectively ($p=0.566$, 95% CI=1.130-1.549). Similarly, there was no significant difference in hr-HPV DNA clearance between the unvaccinated and vaccinated groups 6 months post-procedure, with negative rates of 85.1% vs. 75.5% and positive rates of 14.9% vs. 24.5%, respectively ($p=0.217$, 95% CI=1.412-1.750). The 6-month post-procedure cervical cytology and hr-HPV DNA status of the unvaccinated and vaccinated groups are summarized in Table 2.

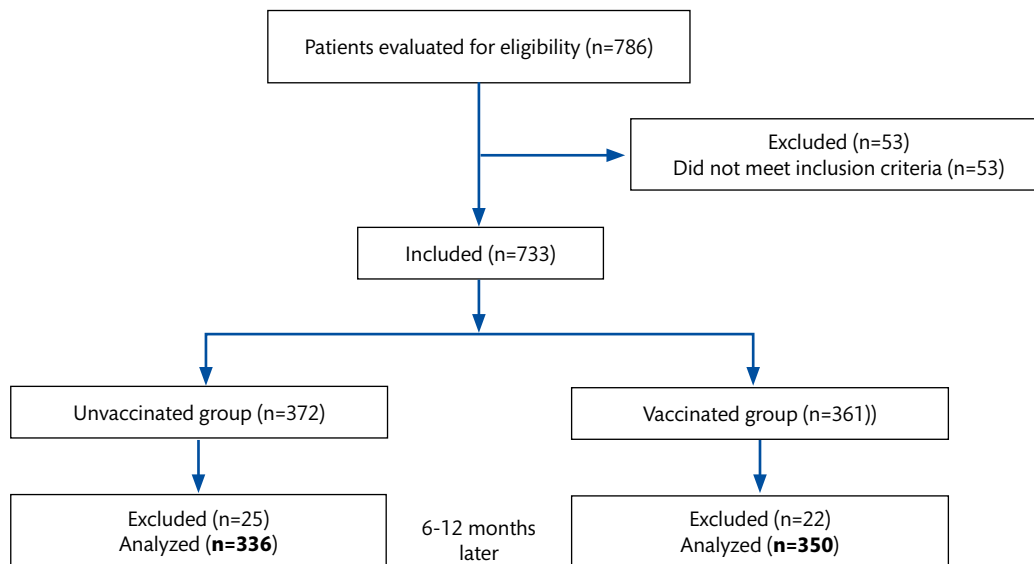


Figure 1. Patient Selection Flow Chart

Table 1. Demographic and clinicopathological data of the unvaccinated and vaccinated groups

		COVID-19 Vaccine		P value
		No (n=350)	Yes (n=336)	
Characteristics		Mean $\pm$ SD	Mean $\pm$ SD	
Age, (years, range)		35 $\pm$ 6.92	33 $\pm$ 5.48	0.588
Parity, (range)		2.12 $\pm$ 1.30	1.91 $\pm$ 1.04	0.464
		n (%)	n (%)	
Smoking		236 (67.4)	207 (61.6)	0.319
Oral contraceptive use		150 (42.9)	132 (39.2)	0.315
Menopause		62 (17.7)	69 (20.5)	0.398
STDs		88 (25.1)	101 (30.3)	0.417
Low socio-economics status		133 (38)	120 (35.7)	0.510
Cervical cytology	Benign	44 (12.6)	56 (31.3)	0.428
	AS-CUS/LSIL	154 (44)	142 (58.8)	
	ASC-H/AGC/HSIL	114 (32.6)	99 (5.8)	
	Unknown	38 (10.8)	39 (11.6)	
HPV	16	98 (28)	84 (25)	0.655
	18	32 (9.1)	30 (8.9)	
	16 and 18	42 (12)	54 (16.1)	
	Non-16/18	136 (38.9)	140 (40)	
	Unknown type	42 (12)	26 (7.7)	
Cervical biopsy	Normal	17 (4.8)	15 (4.5)	0.302
	CIN 1	33 (9.4)	30 (8.9)	
	CIN 2	169 (48.4)	189 (56.3)	
	CIN 3	131 (37.4)	102 (36.3)	
Endocervical curettage ¹ (colposcopy)	Normal	141 (40)	156 (46.4)	0.610
	CIN 1	24 (6.8)	29 (8.6)	
	CIN 2	18 (5.1)	21 (6.3)	
	CIN 3	16 (4.6)	13 (3.9)	
	Insufficient sample	140 (40.3)	117 (34.8)	
Type of excisional procedure	LEEP	79 (22.6)	56 (16.6)	0.734
	Conization	271 (77.4)	280 (83.6)	
Excisional procedure result	Normal	41 (11.7)	54 (16.1)	0.237
	CIN 1	124 (35.4)	105 (31.3)	
	CIN 2	147 (42)	114 (33.9)	
	CIN 3	68 (19.4)	63 (18.7)	
Endocervical curettage ² (excision)	Normal	128 (36.6)	164 (48.9)	0.198
	CIN 1	31 (8.8)	35 (10.4)	
	CIN 2	17 (4.8)	29 (8.6)	
	CIN 3	12 (3.5)	10 (2.9)	
	Insufficient sample	162 (46.3)	127 (37.8)	
Surgical margin	Negative	318 (90.8)	297 (88.4)	0.594
	Positive	32 (9.2)	39 (11.6)	

¹Endocervical curettage at colposcopy²Endocervical curettage during excisional procedure

Chi-square test; p: Significance value; p<0.05; n: Number of patients; Mean: Average; SD: Standard Deviation

STDs: Sexually Transmitted Diseases; AS-CUS: Atypical Squamous Cells of Undetermined Significance; LSIL: Low-grade Squamous Intraepithelial Lesion; HSIL: High-grade Squamous Intraepithelial Lesion; AGC: Atypical Glandular Cells; ASC-H: Atypical Squamous Cells, cannot exclude HSIL; CIN: Cervical Intraepithelial Neoplasia; hr-HPV: High-risk Human Papilloma Virus

Table 2. Cervical Cytology and hr-HPV Results Post-Excisional Procedure

Characteristics		COVID-19 Vaccine		95% CI	P value
		No (n, %)	Yes (n, %)		
Cervical Cytology	Benign	176 (50.3)	161 (47.9)	1.130-1.549	0.566
	AS-CUS/LSIL	98 (28)	106 (29)		
	ASC-H/AGC/HSIL	44 (12.6)	54 (14.7)		
	Unknown	32 (9.1)	15 (4.1)		
hr-HPV	Negative	298 (85.1)	277 (75.5)	1.412-1.750	0.217
	Positive	52 (14.9)	69 (24.5)		
	16	18 (5.2)	17 (5.1)		
	18	8 (2.3)	10 (3)		
	16 and 18	4 (1.1)	7 (2.1)		
	Non-16/18	22 (6.3)	35 (10.4)		

Chi-square test; p: Significance value; p < 0.05; CI: Confidence Interval

AS-CUS: Atypical Squamous Cells of Undetermined Significance; LSIL: Low-grade Squamous Intraepithelial Lesion; HSIL: High-grade Squamous Intraepithelial Lesion; AGC: Atypical Glandular Cells; ASC-H: Atypical Squamous Cells, cannot exclude HSIL; hr-HPV: High-risk Human Papilloma Virus

DISCUSSION

Our study found no significant difference between the cervical cytology and hr-HPV DNA persistence results of unvaccinated and vaccinated patients 6 months post-cervical excisional procedure. The persistence rate of hr-HPV DNA after excision ranges from 2% to 69.3%, varying due to differences in cervical biopsy pathology, patient age, follow-up duration, and hr-HPV DNA type (5),(6).

Costa et al. reported an hr-HPV persistence rate of 36.5% in a 2.4-39.2 month follow-up after excision (7). Bodner et al. reported an hr-HPV DNA rate of 27% at 3 months post-conization (8). Kreimer et al. showed a persistence rate of 75-105% for hr-HPV DNA in patients with CIN1-3 biopsy results following excisional procedures (9). Livasy et al. demonstrated an increasing persistence of hr-HPV DNA infection with extended follow-up duration (22% at 6 months, 31% at 12 months, and 32% at 24 months) (10). In our study, the hr-HPV DNA persistence rate was 14.9% in unvaccinated and 14.6% in vaccinated patients 6 months post-excision. Our study is one of the few investigating the effect of COVID-19 vaccination on hr-HPV persistence post-cervical excisional procedure, finding no association between vaccination and hr-HPV persistence.

The value of HPV genotype as a risk factor for hr-HPV DNA persistence post-treatment is debated. Zang et al. and Bogani et al. reported reduced HPV clearance for HPV 16/18 positive cases compared to other HPV types (11),(12). In contrast, So et al. found no relationship between HPV type and post-excision HPV persistence (13). Similarly, our study did not find an association between hr-HPV DNA type and post-excision HPV persistence. Ayhan et al. also

reported no effect of COVID-19 vaccination, history of SARS-CoV-2 infection, or medication for SARS-CoV-2 on HPV persistence and cytology results (14).

The study's strengths include its single-center design allowing standardization, sufficient sample size, excisional procedures performed by a gynecological oncology team, and pathology results evaluated by experienced pathologists. The main limitation is its retrospective design.

CONCLUSION

This study found no significant difference in cervical cytology and hr-HPV DNA persistence results between vaccinated and unvaccinated patients for COVID-19 6 months post-cervical excisional procedure. Our study is among the few on this topic, and comprehensive studies are needed for better interpretation and acceptance of these findings.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

TA contributed to the design of the article, collection of data, MS contributed to the analysis and interpretation of the article, and wrote the main text.

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