Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1696147

Cervical Human Papilloma Virus Infection and Cytological Abnormalities in Solid-Organ Transplant Recipients: A Study of Screening and Clinical Outcomes

Solid Organ Transplant Alıcılarında Servikal Human Papilloma Virüsü Enfeksiyonu ve Sitolojik Anormallikler: Tarama ve Klinik Sonuçlara İlişkin Bir Çalışma

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ABSTRACT

Aim: This study's objective was to evaluate the outcomes of cervical cancer screening, including human papilloma virus (HPV) testing and cytology, in solid-organ transplantation (SOT) recipients at our institution.

Materials and Methods: The clinical data of 112 patients who underwent SOT were reviewed in this retrospective observational study. The HPV DNA test was conducted using the Hybrid Capture 2 HPV DNA test (hc2; Qiagen, Hilden, Germany). Cytological and histopathological samples were evaluated by expert gynecological pathologists per the Bethesda system.

Results: Data from 40 patients were included in the analysis. Among the transplant recipients, 27 patients (67.5%) had kidney transplants, and 13 (32.5%) had liver transplants. Four patients (10%) had at least one abnormal test result. Excluding the undetermined significance of atypical squamous cells with a concordance-negative HPV test, the combined rate of HPV positivity or abnormal cytology was 7.5%. The rate of high-grade squamous intraepithelial lesions was 2.5%. Two patients who had HPV DNA other than the 16–18 type had persistent HPV DNA results after the 1-year follow-up.

Conclusion: This study showed that the prevalence of high-risk HPV among unvaccinated Turkish women with SOT was higher than that in the general population. Improving early collaboration between transplantation and gynecology clinics may help reduce HPV rates in SOT recipients.

Keywords: Solid organ transplantation, HPV, Cervical cytological abnormalities

ÖZ

Amaç: Amaç: Bu çalışmanın amacı, kurumumuzdaki solid organ tranplant (SOT) alıcılarında insan papilloma virüsü (HPV) testi ve sitolojisi de dahil olmak üzere serviks kanseri taramasının sonuçlarını değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif gözlemsel çalışmada, SOT uygulanan 112 hastanın klinik verileri incelendi. HPV DNA testi, Hybrid Capture 2 HPV DNA testi (hc2; Qiagen, Hilden, Almanya) kullanılarak yapıldı. Sitolojik ve histopatolojik örnekler, Bethesda sistemine göre uzman jinekopatologlar tarafından değerlendirildi.

Bulgular: Analize 40 hastanın verileri dahil edildi. Transplant alıcıları arasında 27 hasta (%67,5) böbrek nakli, 13 hasta (%32,5) ise karaciğer nakli geçirmişti. Dört hastada (%10) en az bir anormal test sonucu vardı. Önemi belirsiz atipik skuamöz hücreler hariç tutulduğunda, HPV pozitifliği veya anormal sitoloji oranı %7,5, yüksek dereceli skuamöz intraepitelyal lezyon oranı %2,5 olarak bulundu. HPV DNA'sı 16-18 tipi dışında pozitif olan iki hastada, 1 yıllık takipten sonra HPV DNA sonuçları persiste ediyordu.

Sonuç: Bu çalışma, aşılanmamış SOT'lu Türk kadınları arasında yüksek riskli HPV prevalansının genel popülasyondan daha yüksek olduğunu göstermiştir. Transplantasyon ve jinekoloji klinikleri arasındaki iş birliğinin erken dönemde oluşturulması, SOT alıcılarında HPV oranlarının azaltılmasına yardımcı olabilir.

Anahtar Kelimeler: Solid organ transplantasyonu, HPV, Servikal sitolojik anormallikler

Cite as: Tiryaki Guner G, Sarioglu C, Aydın O, Ari D, Tastemur S, Akdogan Kayhan M et al. Cervical Human Papilloma Virus Infection and Cytological Abnormalities in Solid-Organ Transplant Recipients: A Study of Screening and Clinical Outcomes. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2026;23(1):94–99.

Geliş/Received: 01.08.2025 • **Kabul/Accepted:** 05.12.2025

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Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

The risk of malignancies, particularly those related to viral infections and pre-invasive lesions, is significantly elevated among solid-organ transplant (SOT) recipients (1-3). This increase has been attributed to factors such as extended life expectancy, aging, and impaired cell-mediated immunity against human papillomavirus (HPV) due to prolonged immunosuppressive therapy (2-4). Meeuwis et al. reported that the incidence of anogenital malignancies over 40 years was 1.6% among renal transplant recipients, higher than that in the general population (5). Additionally, Suwalska et al. found that the progression from HPV infection to high-grade preinvasive lesions or cancer was more rapid in organ transplant recipients than in the general population (6). However, some studies have found no significant difference in the incidence of cervical cancer or HPV positivity between SOT recipients and the general population (7,8). However, the majority of insights into immunocompromised individuals stem from studies primarily focused on HIV-positive populations. Despite this issue's rarity and being a relatively underexplored area, prevention strategies for SOT recipients often mirror those recommended for the general population or remain identical to those for the general population in many countries (9). This study's objective was to assess the outcomes of cervical cancer screening, including HPV testing and cytology, in SOT recipients at our institution.

MATERIALS AND METHODS

The clinical data of 112 patients who underwent solid-organ transplantation in transplantation clinic between April 2019 and September 2024 and who had at least one screening test result were retrospectively reviewed from our institution's electronic database. Our institution is a leading center for both transplantation and oncology in the country. Liver and kidney transplants were performed by highly experienced surgeons specializing in transplantation within the departments of gastroenterological surgery and urology, respectively. Post-transplant follow-up care was provided by gastroenterology specialists in the gastroenterology clinic. This study received approval from the Institutional Ethics Committee (approval number: E2/23/4065), and all patients gave written informed consent for the use of their clinical data. The exclusion criteria included patients with vaginismus (1), those who had undergone hysterectomy (2), those lost to follow-up (2), patients who had never engaged in sexual intercourse (10), deceased patients (16), and male patients (23). Additionally, 18 patients were contacted by phone but declined to attend the gynecological examination. Cytological and histopathological samples were evaluated according to the Bethesda system, the standard reporting model for cervicovaginal cytology, by expert gynecological pathologists (10). Also, HPV DNA test was conducted using the QiaScreen HPV PCR test, which detects 15 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 67and 68; hc2; Qiagen Rotorgene Q, Hilden, Germany). Partial genotyping was performed, where HPV 16 and HPV 18 were reported separately, while other high-risk HPV types were identified as a group. The control repeat tests were conducted in the same laboratory by using same test for entire cohort Ultimately, data from 40 patients were included in the analysis. There are no clear national guidelines or standardized data for cervical cancer screening in transplant recipients, who represent a special population. As a result, the timing of follow-up tests is not uniform and is largely determined by the specialist's clinical judgment. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0 (IBM Inc., Armonk, NY, USA). Continuous variables are presented as medians and ranges (min–max), while categorical variables are presented as frequencies and percentages.

RESULTS

The median age of the cohort was 46 years, ranging from 21 to 67 years. Among the transplant recipients, 27 patients (67.5%) received kidney transplants, and 13 (32.5%) received liver transplants. None of the patients were vaccinated with the HPV vaccine. In total, 36 patients (90%) had both negative HPV DNA and cytology results, with no evidence of intraepithelial lesions or malignancies, and 4 (10%) had at least one abnormal test result (Table).

Additionally, four patients (10%) showed abnormal cytology findings. One patient (Case 1≠) had a negative HPV DNA test but exhibited atypical squamous cells of undetermined significance (ASCUS) in cytology. However, at the 36-month follow-up, the control co-test (HPV DNA and cytology) was negative for both (Case 1≠). Excluding ASCUS with negative concordance, the combined rate of HPV positivity or abnormal cytology was 7.5%.

Specifically, two patients (5%) tested positive for HPV DNA and exhibited ASCUS in cytology (Cases 2≠ and 3≠). Both patients tested positive for HPV types other than 16 or 18. Another patient (Case 4≠) presented with a low-grade squamous intraepithelial lesion (LSIL) in cytology, but no HPV DNA test was conducted due to her being under 25 years of age. Three patients underwent colposcopy, and cervical biopsies revealed chronic cervicitis in two patients (Cases 2≠ and 3≠). Meanwhile, one patient (2.5%) was diagnosed with a high-grade squamous intraepithelial lesion (HSIL) (Case 4≠). Loop electrosurgical excision was performed on Case 4≠, and histopathological examination confirmed the LSIL. This

Table. The findings of patients with SOD and abnormal at least one of the cervical screening test

Case	Age	Transplanted organ	First HPV test result	HPVDNA type	First cytology result	Colposcopic cervical biopsy results	Excisional procedure	Result of excisional procedure	Control results	Follow up time
1	37	Liver	HPV test negative	-	ASCUS	-	-	-	Both tests negative	36 months
2	46	Kidney	Positive HPV	Other than HPV 16-18	ASCUS	Chronic cervicitis	-	-	Persistent HPV (other than HPV16-18) with normal× cytology	13 months
3	38	Kidney	Positive HPV	Other than HPV 16-18	ASCUS	Chronic cervicitis	-	-	Persistent HPV (other than HPV16-18) with normal× cytology	12 months
4	21	Kidney	-	-	LSIL	HSIL	LEEP	LSIL	-*	13 months Lost to follow up

*the time for control human papilloma virus (HPV) or cytology test not completed, LSIL: low grade squamous intraepithelial lesion, HSIL: high grade squamous intraepithelial lesion, ASCUS: atypical squamous cells of undetermined significance
× normal cytology: negative for intraepithelial lesion or malignancy

patient was classified as HPV DNA-positive, which contributed to an overall HPV DNA positivity rate of 7.5%. Two patients (Case 2≠ and Case 3≠) who had HPV DNA other than the 16–18 type had persistent HPV DNA results after the 1-year follow-up. The follow-up period for Case 4≠ was 13 months, respectively. Case 4≠ was contacted by phone but declined to attend the control.

Among the patients who initially tested negative for HPV DNA, six underwent a follow-up test between 12 and 18 months after transplantation, with all maintaining their HPV-negative status. Similarly, another eight patients were retested between 18 and 24 months post-transplantation, and none showed any signs of new HPV infection.

Additionally, among those with negative HPV DNA in the first evaluation, at least 36 months had passed since both the initial HPV DNA test and transplantation surgery in nine SOT recipients. However, two patients were lost to follow-up. Seven patients had control tests (both HPV DNA and cytology), all of which remained negative after 3 years post-transplant.

DISCUSSION

Human papillomavirus (HPV) is the most widespread sexually transmitted infection across the globe (11). Among the diverse HPV strains, high-risk variants—especially types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68—are most closely linked to the development of cancers (12). Other strains, such as HPV types 53, 66, 70, 73, and 82, are also classified as potential high-risk types. In particular, HPV 16 and 18 are the predominant types implicated in the formation of preinvasive lesions and the onset of cervical cancer (13). The persistence of an HPV infection is a key factor driving the progression of anogenital cancers (14), with the host's immune response playing a critical role in determining whether the infection will resolve or persist, ultimately influencing the cancer risk.

SOT recipients rely on immunosuppressive therapy to prevent organ rejection, but this life-saving intervention comes at a cost: a compromised immune system that may struggle to clear HPV infections, heightening the risk of progression to dysplasia or cancer (12, 15-17). Veroux et al. highlighted that vulnerability, reporting that 50% of kidney transplant recipients tested positive for hrHPV, despite having negative hrHPV results during the pre-transplant dialysis period, where testing was conducted every six months (18). Origani et al. found that the incidence of cervical HPV infection among transplant recipients ranged from 10.5% to 27.7% over a ten-year follow-up period (19). A Danish study revealed a 9.3% hrHPV prevalence in renal transplant recipients, which was lower than the 29.4% observed in bone marrow transplant recipients, although the difference was not statistically significant (20). This discrepancy was attributed to the more aggressive immunosuppressive regimens required for the latter group (20). Most patients (75%) were HPV-negative at the three-month post-transplant follow-up, though 10% experienced persistence (20). Reinholdt et al. further

quantified that the risk of anogenital cancers—encompassing the cervix, vulva, vagina, and anus—was significantly elevated in renal transplant recipients compared with the general population, with the risks being 2, 16, 35, and 51 times higher, respectively (21). Additionally, the incidence of cervical HSILs in renal transplant recipients under 40 years of age at the time of transplantation was reported to be 10-15% within 20 years post-transplant, a rate considerably higher than that observed in women without a history of transplantation (21). Ring et al. identified a two-fold increased risk of HPV infection in kidney transplant recipients compared with immunocompetent controls, though the age-specific prevalence of hrHPV infection did not significantly differ (22). Supporting this, Parra Avila et al. reported a 33.3% hrHPV prevalence and a 17.7% rate of cervical intraepithelial lesions among Mexican renal transplant recipients, figures markedly higher than those of the general population (23). However, the median age of their cohort was younger than in other studies (8,9,22,24) and our study. The younger age may partly explain these heightened rates. Some studies challenge the notion of increased HPV prevalence among SOT recipients, revealing no significant difference when compared with the general or immunocompetent population (7,8,19,25). Miyaji et al. also observed no significant difference in the overall HPV prevalence between SOT recipients and immunocompetent individuals (7). However, they indicated a striking disparity in hrHPV rates, with the SOT group showing a significantly higher prevalence (19.4% vs. 7.4%) (7). Mazanowska et al. found comparable hrHPV infection rates between kidney transplant recipients and healthy women (25). In our study, the hrHPV prevalence was identified as 7.5%. Comparing studies from varied countries and populations is not simple, as the unique demographics and cultural contexts create significant disparities. A large-scale study of one million Turkish women reported an HPV DNA positivity rate of 3.2% within the general population (26). In contrast, our study revealed a notably higher HPV DNA positivity rate among SOT recipients, surpassing that observed in the broader population of Turkey. None of the patients who initially tested negative for both HPV and cytology and had control tests after a follow-up period of at least 12 months developed a new HPV infection in our study. Two patients had persistent HPV infection. One patient had a transient smear abnormality.

An increasing number of publications, including prospective studies, shed light on the screening of cervical cancer in people with human immunodeficiency virus (HIV), which is one of the immunocompromised conditions. However, despite growing awareness, research remains limited for many other immunocompromised groups, leaving significant gaps in our understanding and preventive strategies. Therefore, many guidelines and national protocols manage SOT patients based on recommendations originally designed for individuals with HIV which are different from general population (15). World health organization recommended that patient with HIV should be screened in different intervals from general population that was every 3-5 years (27). According to report published in 2023, after considering studies collectively, it was observed that HPV screening every three years, with appropriate triage, for women living with HIV offers comparable effectiveness to five-yearly HPV screening in the general population, yielding similar reductions in cervical cancer burden and overall efficiency (28). The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends initiating screening within one year of the first insertive sexual activity for patients with solid organ transplants (SOT), which differs from the general population's recommendation of starting screen at age 21, regardless of sexual activity (29). Screening should be performed annually for the first three years, then every three years with cytology alone until the age of 30. After 30, patients may either continue with cytology alone or undergo co-testing every three years (29). In our country, cervical cancer screening begins at age 21 with cytology every three years, transitioning to primary HPV testing with genotyping triage using cytology after age 30. While the findings of this study do not establish a definitive recommendation for the national screening program for immunosuppressed patients, that highlights the importance of close follow-up and encourage consideration of international guidelines for those, including SOT.

The prevalence of hrHPV types among transplant recipients varies across studies (5,17,20,22,24,30). Consistent with some previous studies (20,24), our research revealed that the predominant HPV types were those other than HPV 16 or 18. While many studies rank the top three HPV types in transplant recipients as those covered by the nonavalent HPV vaccine, the effectiveness of these vaccines in immunosuppressed individuals remains a subject of ongoing debate. Limited research has explored this area, but existing studies suggest suboptimal seroconversion rates in patients with SOT (31-33). For instance, Kumar et al. and Boey et al. reported seroconversion rates to HPV vaccines ranging between 50% and 70%, varying by HPV type (31,32). Given that the most common HPV types in transplant recipients are included in HPV vaccines, and the majority of patients remain HPV-negative at the time of transplantation, this gap must be addressed. The lack of vaccination may be influenced by multiple factors such as costs, awareness, national policy as it is still not included in the national childhood vaccination program, hesitancy among patients or some caregivers. To raise awareness of vaccination, national-level meetings and seminars are organized to inform both patients and healthcare professionals. However, cost is a major barrier to the widespread adoption of vaccination and limit the access. Furthermore, with studies highlighting reduced immunogenicity in this population, integrating the HPV vaccine into

the childhood national immunization program is a critical step in addressing this issue. Additionally, transplant clinics must prioritize pretransplantation vaccination, especially in countries where the HPV vaccine is not part of the national immunization program. This proactive approach is particularly relevant for transplantation clinics managing patient months ahead of transplantation, ensuring optimal protection before immunosuppression begins.

The primary limitations of this study lie in its retrospective design and relatively small sample size. The retrospective nature of this research also resulted in incomplete data, particularly regarding patient demographics and detailed histories of prior immunosuppressive treatments. This retrospective study on patients undergoing solid organ transplantation (SOT) that presented to transplantation clinic minimizes selection bias by not being limited to those presenting to a gynecologic oncology clinic. Additionally, despite all efforts and telephone contact attempts, some patients refused to return for follow-up visits, highlighting the limitation of patient loss to follow-up. Because of the retrospective design and including specific population, long-term follow-up data were limited. In spite of that, our study provides valuable real-world insights into HPV infection dynamics in this specific patient population (SOT recipients). Additionally, previous studies have shown that early HPV persistence patterns can be predictive of long-term outcomes, supporting the clinical relevance of our findings. To the best of our knowledge, this study provides unique insights into HPV prevalence, cytology findings, and cervical lesions in Turkish women with SOTs, a population that has not been extensively studied before in our country. Therefore, as one of the first studies of its kind in Turkey, this research provides a foundation for national policies and guidelines. Its other strengths are the cytological and histopathological evaluations performed by expert gynecological pathologists, ensuring reliable and standardized diagnoses. This study utilized data from a leading transplantation and oncology center in our country. Colposcopic evaluations were also performed by experienced gynecological oncologists.

CONCLUSION

This study showed that the prevalence of hrHPV among unvaccinated Turkish women with SOT was higher than that in the general population. Enhancing clinicians' awareness of tailored prevention and follow-up strategies, combined with fostering stronger collaboration between transplantation and gynecological clinics in earlier pretransplantation periods, may contribute to reducing HPV rates among SOT recipients. Future prospective studies with larger sample sizes and extended follow-up periods are needed to further validate our findings and provide a more comprehensive understanding of HPV prevalence and its clinical implications in SOT recipients.

Conflict of interest statement: The authors declare no conflicts of interest.

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