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Initial prevalence of anal human papilloma virus infection in liver transplant recipients

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Summary

Although liver transplant recipients are at increased risk of human papilloma virus (HPV)-related anal cancer, limited data are available regarding the initial prevalence of anal HPV infection in this population. Anal swabs collected from 50 liver transplant recipients within the first three postoperative weeks were subjected to real-time polymerase chain reaction for detection of the four HPV genotypes: 6, 11, 16, and 18. Predictors of any, low-risk, and high-risk anal HPV infection were evaluated. Overall, the prevalence of any anal HPV infection was 18.0%, with the corresponding rates for high- and low-risk HPV genotypes being 8.0% and 10.0%, respectively. Infection with any type of anal HPV was higher in patients with hepatitis B virus (HBV) infection ($P = 0.027$), ≥3 sexual partners ($P = 0.031$), and alcoholic liver disease ($P = 0.063$). HBV infection was the only factor significantly associated with high-risk HPV infection ($P = 0.038$). Male sex ($P = 0.050$), age ≥52 years ($P = 0.016$), ≥30 sexual partners ($P = 0.003$), age at first intercourse ≤18 years ($P = 0.045$), and time since first intercourse ≥38 years ($P = 0.012$) were identified as predictors of low-risk HPV infection. These results indicate that HPV vaccination of liver transplant candidates and screening for anal HPV infection in high-risk groups should be considered.

Introduction

Infection with the human papilloma virus (HPV) is one of the most common forms of sexually transmitted diseases (STDs) worldwide [1,2]. Persistent HPV infection is associated with increased risk of developing several types of malignancies, particularly those of the anogenital region. Based on their oncogenic potential, the HPV genotypes are classified into the low-risk group, which comprises the HPV genotypes 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, and 81, or the high-risk group, which comprises HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 [3]. In contrast to the latter, infection with low-risk HPV genotypes is commonly considered as not predisposing to the development of high-grade lesions or invasive cancers, however, may lead to the development of genital warts or low-grade intraepithelial neoplasia [4].

Anal cancers are considered rare neoplasms, with an incidence reported to range from 0.7 to 1.9/100 000 population [5,6]. However, recently published data from the Surveillance, Epidemiology and End Results (SEER) Program indicate a rapidly rising incidence of anal tumors in the United States, characterized by an annual increase of 3.6% and 2.3% in men and women, respectively, over a nearly 30-year period [7]. The association between HPV infection and development of anal cancer appears specific for the squamous-cell cancer histological type [3]. Rate of anal cancers related to persistent infection with high-risk HPV

genotypes is estimated at approximately 90%. Of all the high-risk HPV genotypes, HPV 16 and 18 are responsible for the vast majority of these tumors [8,9].

Solid organ transplant recipients are at increased risk of developing malignant tumors due to the necessity for long-term immunosuppression. Overall, this patient population faces a twofold elevation in cancer risk compared with the general population, with the highest standardized incidence ratios reported for Kaposi sarcoma, lip cancer, nonmelanoma nonepithelial skin cancer, and liver cancer [10]. Solid organ transplant recipients have also been reported to have a higher risk of all HPV-related cancers, except for invasive cervical cancer, than the general population. Notably, anal cancer has been found to be the second most frequent HPV-related tumor, just after the vulvar cancer, to develop after solid organ transplantation [11]. Accordingly, immunosuppression and anal HPV infection seem to synergistically increase the risk of anal cancer in the post-transplant period.

Although the development of anal cancer has not been completely characterized, it appears to resemble that of cervical cancer [3]. Therefore, given the efficacy of prevention and screening for the latter [12–14], similar strategies might be useful for decreasing the risk of the former. However, besides a single report by Roka *et al.* from 2004 [15], the literature on transplantations is void of any data regarding anal HPV infection in liver transplant recipients. As such data are of essential importance with respect to the design of prevention and screening strategies, the purpose of this study was to help fill this research need by evaluating the initial prevalence of anal HPV infection in liver transplant recipients and potentially, identifying high-risk groups for anal HPV infection.

Patients and methods

This study was performed between June 2012 and August 2013 in the Department of General, Transplant and Liver Surgery at the Medical University of Warsaw, the largest liver transplant center in Poland with a total of 1367 liver transplantation procedures performed as of December 2013. The study group comprised 50 primary liver transplant recipients (25 men and 25 women). Only a history of previous liver transplantation was set as an exclusion criterion. None of the patients received HPV vaccination. The study protocol was approved by the local ethics committee of the Medical University of Warsaw (and have therefore been performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008), and informed consent was obtained from each study participant prior to inclusion.

Patients were enrolled during the 3-week hospitalization period following primary liver transplantation (median of 9 days). Samples were collected from the anal canal and perianal area (a simple swab, first of the anal canal, and then of the perianal area) using flocked plastic shaft polyester applicator swabs and stored in 3 ml of transport medium containing Hank's balanced salt solution, bovine serum albumin, cysteine, gelatin, sucrose, glutamic acid, HEPES buffer, vancomycin, amphotericin B, and colistin (Universal Transport Medium System; Copan Italia S.p.A., Brescia, Italy). Specimens were frozen at −70 °C until further processing. DNA was extracted using the DNA-Sorb-A extraction kit (Sacace Biotechnologies S.r.l., Como, Italy). The presence of high-risk HPV genotypes 16 and 18 and low-risk HPV genotypes 6 and 11 was assessed quantitatively by real-time polymerase chain reaction (RT-PCR) using the Sacace TV12-100FRT and TV11-100FRT tests (Sacace Biotechnologies S.r.l.), respectively. Multiplex real-time amplification was performed in a SmartCycler (Cepheid, Sunnyvale, CA, USA).

To collect data regarding sexual activity, patients were requested to complete a brief questionnaire consisting of four questions concerning sexual orientation, age at first sexual intercourse, lifetime number of sexual partners, and history of STDs. Data regarding post-transplant immunosuppression and the cause of liver disease, particularly hepatitis C virus (HCV) and hepatitis B virus (HBV) infection and alcoholic liver disease (ALD), were obtained from patient medical records. History of HCV or HBV infection was defined as the presence of anti-HCV antibodies and the presence of either hepatitis B surface antigen or antihepatitis B core antibodies, respectively. To maintain confidentiality and privacy, each patient was assigned a unique number used for coding of the anal specimens, questionnaires, and medical records. Patients were requested to independently insert their completed questionnaires into a sealed black box to be opened at the conclusion of the study.

Quantitative and qualitative variables were presented as medians (ranges) and numbers (percentages), respectively. Fisher's exact test and Mann–Whitney *U*-test were used for conducting comparisons, as appropriate. Receiver operating characteristics (ROC) curves were developed to determine the most appropriate cutoff values for quantitative variables in predicting the presence of HPV infection. The level of statistical significance was set at 0.05; STATISTICA version 10 software (StatSoft Inc., Tulsa, OK, USA) was used to conduct all statistical analyses.

Results

The baseline characteristics of the liver transplant recipients included in the study are presented in Table 1. Of the 50 patients, four patients refused to complete all four items in

Table 1. Baseline characteristics of the 50 patients enrolled in the study.

Factor	*n* (%) or median (range)
Patient sex	
Male	25 (50.0)
Female	25 (50.0)
Patient age	48.5 (19–66)
Hepatitis C virus infection	14 (28.0)
Hepatitis B virus infection	12 (24.0)
Alcoholic liver disease	6 (12.0)
Primary sclerosing cholangitis	7 (14.0)
Primary biliary cirrhosis	6 (12.0)
Autoimmune hepatitis	10 (20.0)
Sexual orientation*	
Heterosexual (males/females)	19 (95.0)/20 (95.2)
Bisexual (males/females)	1 (5.0)/1 (4.8)
Homosexual (males/females)	0 (0.0)/0 (0.0)
Number of sexual partners†	2 (0–200)
Age at first sexual intercourse†	20 (15–36)
Time since first sexual intercourse†	30 (0–48)
History of sexually transmitted diseases†	1‡ (2.2)
Basiliximab for induction	38 (76.0)
Immunosupressive regimen based on tacrolimus and steroids	35 (70.0)
Other immunosuppressive regimens:	
Tacrolimus + MMF + steroids	11 (22.0)
MMF + steroids	3 (6.0)
Tacrolimus + steroids + azathioprine	1 (2.0)

MMF, mycophenolate mofetil.
*Five male and four female patients refused to declare their sexual orientation.
†Four patients refused to fill the entire questionnaire.
‡Gonorrhea.

the questionnaire, five refused to answer the item regarding their sexual orientation, and one refused to answer the item regarding the number of previous sexual partners. None of the patients gave a reason for their refusal to complete one or more items. The prevalence of infection with any HPV genotype (6, 11, 16, or 18) was found to be 18.0% (9 of 50), with the high-risk genotypes (16 or 18) to be 8.0% (4 of 50) and with the low-risk genotypes (6 or 11) to be 10.0% (5 of 50). By genotype, the prevalence of HPV infection was 6.0% (3 of 50) for genotype 16, 2.0% (1 of 50) for genotype 18, 8.0% for genotype 6 (4 of 50), and 2.0% (1 of 50) for genotype 11. No patient was infected with multiple HPV genotypes.

Hepatitis B virus infection was significantly associated with increased prevalence of infection with any HPV genotype ($P = 0.027$), as well as with high-risk HPV infection ($P = 0.038$; Table 2). All low-risk HPV infections were detected in male patients (5 of 25; 20.0%; $P = 0.050$). Moreover, a tendency toward higher frequency of any HPV infection was detected in patients with ALD ($P = 0.063$). While anal HPV 16 infection was detected in one male patient who identified himself as bisexual, none of the analyzed HPV genotypes were detected in a woman who identified herself as bisexual. Low-risk HPV 6 anal infection was also detected in one male patient with a history of gonorrhea. There were no differences in anal HPV detection rates with respect to the type of immunosuppressive regimen.

Presence of any HPV infection was significantly associated with a higher number of sexual partners ($P = 0.020$) and tended to be associated with younger age at the time of first sexual intercourse ($P = 0.074$; Table 3). Similarly, a higher number of sexual partners ($P = 0.022$), younger age at the time of first sexual intercourse ($P = 0.016$), and longer time between first sexual intercourse and liver transplantation ($P = 0.031$; Table 4) were significantly associated with the presence of low-risk HPV infection. Additionally, patients with low-risk HPV infections tended to be older ($P = 0.065$). No significant associations were observed between high-risk HPV infection and number of sexual partners, age at first sexual intercourse, time since first sexual intercourse, or patient age. Duration of immunosuppression was not related to any type of HPV infection.

The optimal cutoff values for the number of sexual partners and age at the time of first sexual intercourse to predict presence of infection with any HPV genotype were found to be three or more and 19 years or younger, respectively (Fig. 1). Accordingly, the prevalence of infection with any HPV genotype was found to be 27.8% (5 of 18) in patients with three or more sexual partners compared with 3.7% (1 of 27) in patients with fewer than 3 ($P = 0.031$), and 25.0% (5 of 20) in patients aged 19 years or younger at the time of first sexual intercourse compared with 7.7% (2 of 26) in patients older than 19 years ($P = 0.213$). Regarding the detection of low-risk HPVs, the optimal cutoff values were 30 or more for the number of sexual partners, 18 years or younger for age at the time of first sexual intercourse, 52 years or older for current age, and 38 years or more for the time since first sexual intercourse (Fig. 2). Specifically, the prevalence of low-risk HPV infection was found to be 66.7% (2 of 3) in patients with 30 or more sexual partners and 0.0% (0 of 42) in patients with fewer than 30 ($P = 0.003$); 17.6% (3 of 17), in patients aged 18 years or younger at the time of first sexual intercourse and 0.0% (0 of 29) in patients older than 18 years ($P = 0.045$); 21.7% (5 of 23), in patients currently aged 52 years or older and 0.0% (0 of 27) in patients younger than 52 years ($P = 0.016$); and 27.3% (3 of 11) in patients 38 years or more since first sexual intercourse and 0.0% (0 of 34) in the remaining patients ($P = 0.012$).

Discussion

To the best of our knowledge, the current study is the first study to examine the prevalence of HPV infection

Table 2. Prevalence of human papilloma virus (HPV) 6, 11, 16, and 18 infections according to patient sex, etiology of liver disease, and immunosuppressive regimen.

	Any HPV (HPV 6, 11, 16, 18)		Low-risk HPV (HPV 6, 11)		High-risk HPV (HPV 16, 18)	
	n (%)	*P*	*n* (%)	*P*	*n* (%)	*P*
Patient sex						
Male (*n* = 25)	7 (28.0)	0.138	5 (20.0)	0.050	2 (8.0)	>0.999
Female (*n* = 25)	2 (8.0)		0 (0.0)		2 (8.0)	
Hepatitis C virus infection						
Yes (*n* = 14)	3 (21.4)	0.697	3 (21.4)	0.126	0 (0.0)	0.566
No (*n* = 36)	6 (16.7)		2 (5.6)		4 (11.1)	
Hepatitis B virus infection						
Yes (*n* = 12)	5 (41.7)	0.027	2 (16.7)	0.582	3 (25.0)	0.038
No (*n* = 38)	4 (10.5)		3 (7.9)		1 (2.6)	
Alcoholic liver disease						
yes (*n* = 6)	3 (50.0)	0.063	2 (33.3)	0.103	1 (16.7)	0.411
no (*n* = 44)	6 (13.6)		3 (6.8)		3 (6.8)	
Primary sclerosing cholangitis						
Yes (*n* = 7)	0 (0.0)	0.325	0 (0.0)	>0.999	0 (0.0)	>0.999
No (*n* = 43)	9 (20.9)		5 (11.6)		4 (9.3)	
Primary biliary cirrhosis						
Yes (*n* = 6)	1 (16.7)	>0.999	0 (0.0)	>0.999	1 (16.7)	0.411
No (*n* = 44)	8 (18.2)		5 (11.4)		3 (6.8)	
Autoimmune hepatitis						
Yes (*n* = 10)	0 (0.0)	0.174	0 (0.0)	0.569	0 (0.0)	0.571
No (*n* = 40)	9 (22.5)		5 (12.5)		4 (10.0)	
Basiliximab for induction						
Yes (*n* = 38)	8 (21.1)	0.425	5 (13.2)	0.319	3 (7.9)	>0.999
No (*n* = 12)	1 (8.3)		0 (0.0)		1 (8.3)	
Immunosuppresive regimen						
Tacrolimus + steroids (*n* = 35)	7 (20.0)	0.705	4 (11.4)	>0.999	3 (8.6)	>0.999
Other (*n* = 15)	2 (13.3)		1 (6.7)		1 (6.7)	

Table 3. Associations between human papilloma virus (HPV) infections and number of sexual partners, age at the time of first sexual intercourse, and patient age.

	Number of sexual partners		Age at first sexual intercourse		Patient age	
	Median (range)	*P*	Median (range)	*P*	Median (range)	*P*
Any* HPV infection						
Yes	7.5 (1–200)	0.020	18 (15–21)	0.074	53 (33–61)	0.272
No	1 (0–75)		20 (16–36)		47 (19–66)	
High-risk† HPV infection						
Yes	4 (1–10)	0.273	19.5 (18–21)	0.876	46.5 (33–55)	0.642
No	2 (0–200)		20 (15–36)		50.5 (19–66)	
Low-risk‡ HPV infection						
Yes	115 (30–200)	0.022	15 (15–18)	0.016	56 (52–61)	0.065
No	2 (0–75)		20 (16–36)		47 (19–66)	

*HPV 6, 11, 16, or 18.
†HPV 16 or 18.
‡HPV 6 or 11.

exclusively in a cohort of liver transplant recipients and by far the largest, providing baseline epidemiological data for further research. Notably, in a 2003 study of 43 renal and 17 liver transplant recipients, Roka *et al.* [15] found the prevalence of any anal HPV infection within 24 postoperative hours to be 20.9% for the former and 29.4% for the

Table 4. Associations between human papilloma virus (HPV) infections and time since first sexual intercourse and duration of immunosuppression.

	Time since first sexual intercourse (years)		Duration of immunosuppression (days)	
	Median (range)	*P*	Median (range)	*P*
Any* HPV infection				
Yes	34 (13–44)	0.294	9 (7–21)	0.696
No	29.5 (0–48)		9 (4–21)	
High-risk† HPV infection				
Yes	28 (13–34)	0.590	10 (7–21)	0.592
No	31 (0–48)		9 (4–21)	
Low-risk‡ HPV infection				
Yes	43 (38–44)	0.031	8 (7–21)	0.999
No	29 (0–48)		9 (4–21)	

*HPV 6, 11, 16, or 18.
†HPV 16 or 18.
‡HPV 6 or 11.

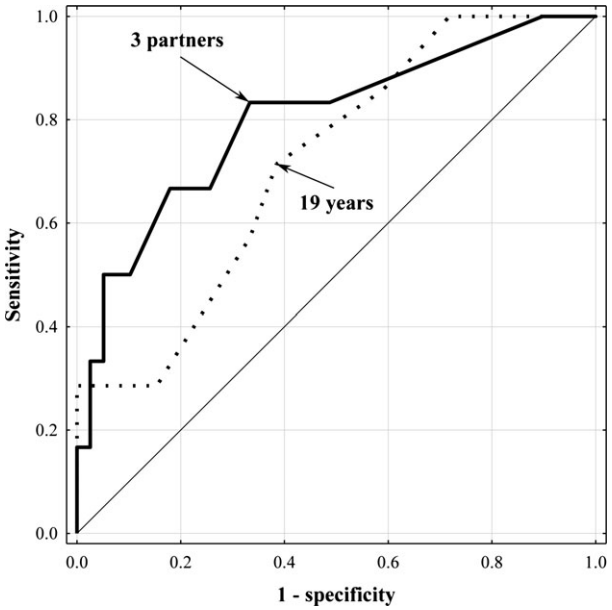

Figure 1 Receiver operating characteristics curves for the prediction of any type of anal human papilloma virus (HPV) infection based on the number of sexual partners (solid line) and age at first sexual intercourse (dotted line).

latter, higher as compared to the 18.0% found in the current study. This difference seems natural as the presented results were limited to the detection of HPV genotypes 6, 11, 16, and 18. However, given the targets of both quadrivalent vaccine (Gardasil for HPV 6, 11, 16, and 18) and bivalent vaccine (Cervarix for HPV 16 and 18) and the fact that the vast majority of anal cancers are related to HPV 16

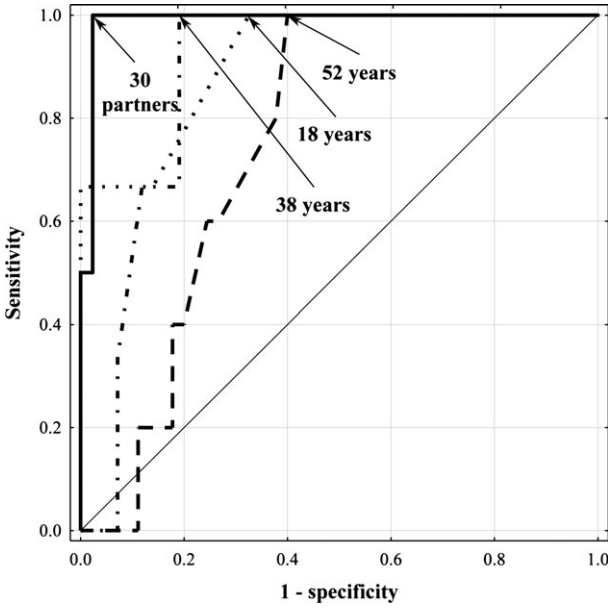

Figure 2 Receiver operating characteristics curves for the prediction of low-risk anal human papilloma virus (HPV) infection based on the number of sexual partners (solid line), age at first sexual intercourse (dotted line), patient age (dashed line), and time since first sexual intercourse (dash-dot line).

and 18 [8,9], these four genotypes appear to be of particular importance in the population of liver transplant recipients.

The prevalence of and risk factors for anal HPV infection have been previously investigated in renal transplant recipients. Patel *et al.* [16] found the prevalence of infection with any HPV genotype to be 21.3% in that population of patients. Among the risk factors identified for anal HPV infection were longer duration of immunosuppression and multiple sexual partners, the second of which accords with the findings of the present study. On the contrary, neither duration nor type of immunosuppression was related with anal HPV detection rates in the present study. This is probably due to the relatively short duration of immunosuppression, practically no chance of acquiring new anal HPV infection since transplant, and the fact that vast majority of patients received similar immunosuppressive regimen.

The only novel risk factor for increased prevalence of high-risk anal HPV 16 or 18 infection identified in the current study was a history of HBV infection. Nevertheless, a history of other STDs, including HBV and HCV infection, was previously found to be associated with seroprevalence of high-risk HPV genotypes 16 and 18 [17]. A history of HCV infection but not HBV infection has also been reported as a risk factor for high-risk cervical HPV infection in liver transplant candidates [18].

The rate of low-risk HPV DNA positivity was found to be significantly higher for male liver transplant recipients

than that for female patients. These findings contrast with those of previous studies, which reported that women as well as men having sex with men (MSM) have a higher risk of anal HPV infection and anal cancer than men having sex with women (MSW) [9,19,20]. Unfortunately, almost no data are available regarding the specific incidence of anal cancer following liver transplantation by recipient sex. Interestingly, there were no cases of post-transplant anal cancer in the data of 1145 liver transplant recipients from the Department of General, Transplant and Liver Surgery of the Medical University of Warsaw [21].

All low-risk anal HPV infections detected in the current study were found in male patients aged 52 years or older. This finding accords with those of the HPV in Men Study, which reported that relatively older age is a risk factor for persistent anal HPV infection in heterosexual men [22]. On the other hand, other authors observed relatively high seropositivity rates for both HPV 6 and 11 in males aged less than 52 years [17]. Notably, although HPV genotypes 6 and 11 are generally considered to have low oncogenic potential, they are occasionally responsible for the development of anal cancer [23,24]. Considering the necessity of life-long immunosuppression in liver transplant patients, surveillance of anal cancer in patients with initial anal HPV 6 and/or 11 infections might be justified.

Other risk factors for anal HPV infection identified in the current study were relatively higher number of sexual partners, younger age at the time of first sexual intercourse and longer time since first sexual intercourse. Notably, number of sexual partners and age of sexual initiation are frequently reported with respect to cervical HPV infection [25,26]. Regarding anal HPV infections, majority of studies were performed in MSM populations, hence reported the number of anal sex partners to be an important risk factor [27,28]. Nevertheless, lifetime number of sexual female partners has also been identified as a risk factor for any anal HPV infection in MSW [29].

The relatively low initial prevalence of HPV 6, 11, 16, and 18 infections in liver transplant recipients might indicate that HPV vaccination, with either bivalent or quadrivalent vaccine, might be a useful strategy in decreasing the risk of *de novo* anal cancer following liver transplantation. This indication is supported by the findings regarding the use of the quadrivalent HPV vaccine, which was found effective in the prevention of persistent anal HPV infection and anal intraepithelial neoplasia in a cohort of healthy MSM [30]. As solid organ transplant recipients are also at increased risk of the development of other HPV-related malignancies [11], the potential benefits of HPV vaccination might be even more pronounced in this population of patients. Thus, further studies evaluating the benefits of HPV vaccination in liver transplant candidates should be pursued to collect data with which to justify large-scale vaccination.

Identification of the specific groups of liver transplant recipients at high risk of anal HPV infection might be useful with respect to the development of potential screening schemes. More specifically, liver transplant candidates with HBV infection should undergo screening for high-risk anal HPV infection. Given that low- and high-risk HPV genotypes share the same transmission route, it may also be considered in patients with higher number of lifetime sexual partners, at older age, younger at the time at first sexual intercourse and with longer time since first sexual intercourse. Unfortunately, the efficacy of screening for anal cancer has not been assessed in randomized clinical trials, most probably due to low absolute numbers of anal cancer cases [13]. Nevertheless, we propose a following protocol for patients undergoing liver transplantation: (i) pretransplant screening for HPV 6, 11, 16, and 18 anal infection in all patients with any of the revealed risk factors; (ii) pretransplant vaccination with quadrivalent vaccine regardless of the screening result (except for patients infected with all four genotypes) in patients younger than 52 years and with at least one risk factor for anal HPV infection; (iii) post-transplant annual performance of anal exfoliative cytology or high-resolution anoscopy in patients with positive pretransplant screening result; (iv) treatment of patients with high-grade lesions with one of the available effective modalities [31].

Several limitations of this study must be acknowledged. First, the relatively modest size of the study group may limit the generalizability of the obtained results. Second, the data on a history of anal intercourse were not collected. Furthermore, collection of additional data regarding sexual history was impossible due to blinded collection of questionnaires. Third, assessment of the four, and not all HPV genotypes, might have led to slight underestimation of the prevalence rates, despite the fact that they are all among the five most prevalent genotypes [22]. Finally, detection of HPV DNA was performed at only one time point during the immediate post-transplant period. Notably, vast majority of anal HPV 6, 11, 16, and 18 infections are transient among nonimmunosuppressed patients [22]. However, among individuals with human immunodeficiency virus infection hence under a setting resembling this of liver transplant recipients under immunosuppression, the HPV 6, 11, 16, and 18 clearance rates are low, ranging from only 12.2 to 20.4 cleared episodes per 1000 person-months [32]. Accordingly, although assessment of HPV infection at single time point might not accurately reflect the risk of the development of anal cancer in general population, it seems relevant for patients requiring life-long immunosuppression.

Authorship

MG, KG, MM, WP and MK: study design. All authors: performance of study. All authors: acquisition of data. MG, MM, SW, GM and MK: interpretation of data. MG and ZL: analysis of data. MG: manuscript writing; all other authors: critical revision of the manuscript.

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