

12-31-2022

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Recommended Citation

Purwoko, Izazi Hari; Karim, Putri Laksmi; Nugroho, Suroso Adi; Toruan, Theresia; and ., Fitriani (2022) "Risk Factors for HIV-positive Status In Condyloma Acuminata," *Journal of General - Procedural Dermatology & Venereology Indonesia*: Vol. 6: Iss. 2, Article 5.

DOI: 10.7454/jdvi.v6i2.1004

Available at: <https://scholarhub.ui.ac.id/jdvi/vol6/iss2/5>

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Abstract

Background: Condyloma acuminata (CA) is a sexually transmitted infection (STI) caused by human papillomavirus (HPV), especially types 6 and 11. The number of HPV infections increases in immunosuppressed conditions, such as human immunodeficiency virus (HIV) infection. Risk factors in CA patients such as gender, sexual partner, sexual orientation, and sexual intercourse can increase HIV status.

Methods: This is a descriptive-analytic study with a cohort retrospective design. The subjects are all CA patients who visited the polyclinic STI Dr. Mohammad Hoesin, General Hospital, Palembang, Indonesia, between 2016-2020. The number of CA patients included in the study were 115 patients aged 14 to 71 years old. Chi-square and multivariate logistic regression were used to analyze the independent variables.

Results: The total number of HIV-positive CA patients was 31 (26.8%) out of 115. There were more males than females, and the mean age was 29 ± 9.90 , with a range of 14-71 years old. The most common location was the genital (58.3%). Gender, marital status, number of partners, sexual orientation, sexual intercourse, location, and type of lesions had $p < 0.05$ in bivariate analysis. Of all men in this study, 43 (60.6%) had sex with men (MSM), and 37 from 43 MSM (86%) had perianal/anal lesions.

Conclusion: Risk factors for HIV in CA patients are age, marital status, sexual partner, sexual orientation, and location of lesions. CA patients who were MSM had a 22-fold higher risk for HIV-positive status.

Keywords: *Condyloma acuminata, Human Immunodeficiency Virus, MSM*

Background

Condyloma acuminata (CA) is a sexually transmitted infection caused by certain types of human papillomavirus (HPV) with a clinical picture of fibroepithelioma on the skin and mucosa. Human papillomavirus (HPV) is a double-stranded DNA virus belonging to the *Papovaviridae* family.¹ Human papillomavirus has more than 150 DNA genotypes. Types 6 and 11 HPV are most commonly found in exophytic CA and low-grade dysplasia (low risk), while HPV types 16 and 18 are often found in high-grade dysplasia and malignancy (high risk).¹⁻³

Condyloma acuminata are also known as genital warts, venereal warts, or anogenital warts (AGW).¹ HPV enters the body through microlesion on the skin and mucosa, so CA often occurs in areas prone to trauma during sexual intercourse.^{3,4} Damage to the mucosa in CA can

facilitate human immunodeficiency virus (HIV) infection, whereas HIV infection predisposes to increased incidence and transmission of CA.⁵⁻⁷ HIV patients are more at risk of developing CA than patients without HIV, and the lesions are more difficult to heal due to decreased cellular immunity.

CA and HIV are related. All persons with sexually transmitted infections (STIs), such as CA, should be screened for HIV routinely, even if the patient has no known sexual behavior risk.⁷ HIV can be transmitted through unprotected sexual intercourse, unsterilized and sharing needles/piercing/tattooing, unsterilized medical equipment, blood transfusions containing HIV, and vertical transmission from an HIV-positive mother to a baby. Certain body fluids can transmit HIV, such as blood, semen, vaginal fluids, and breast milk. Groups at risk for HIV infection include injecting drug users, sex workers and their

customers, men who have sex with men (MSM), and partners from high-risk groups.⁸⁻¹⁰ The risk of malignant dysplasia increases if HIV and HPV infection coincide.^{5,11} The clinical picture of CA may include cauliflower-like papillomatous papules or nodules found on the mucous membranes or skin of the external genitalia, perineum, and anus. Transmission is mainly through sexual contact, either genito-genital, genito-oral or genito-anal.¹⁻³

The prevalence of HPV infection increases in immunosuppressed conditions such as HIV infection, under immunosuppressive therapy, and pregnancy. This situation causes the development of condylomata acuminata lesions to be longer, easy to recur, and larger (giant condyloma). Clinical manifestations are lengthier, and it is difficult to clear the virus, leading to persistent HPV infection.^{3,12} The prevalence of HPV infection is high in MSM, with the most common site of infection being the anus.^{5,12} A retrospective study conducted in Surabaya showed an increase in the number of CA patients with HIV from 2011-2014. In 2011 there were 8 people (0.78%). The year after, there were 7 people (0.79%). In 2013, the number increased by 13 people (1.26%). In 2014, it increased by 35 people (3.09%).¹³

Few studies have been conducted to determine the prevalence and risk factors of CA among HIV-positive in Indonesia. The aim of this study was to describe the prevalence of HIV-positive status in CA patients, to determine high-risk behavior in study participants, and to identify independent risk factors in HIV status of CA patients to recommend future intervention.

Methods

This study is a descriptive-analytic retrospective study. The inclusion criteria were all new CA

patients who visited the Polyclinic of Dr. Mohammad Hoesin General Hospital Palembang from January 2016 to December 2020. The diagnosis of CA was established by an expert dermatologist based on history taking and physical examination.⁷ The diagnosis of HIV status (positive or negative) was determined from laboratory tests.

Data were taken from medical records with exclusion criteria duplication and incomplete data. The dependent variable is HIV status, and independent variables consist of age, gender, marital status, number of sexual partners, sexual orientation, sexual intercourse, CA location, and CA lesion shape.

The data collected was cleaned, edited, coded, and processed using the Statistical Package for the Social Science (SPSS) software version 23.0 (IBM Corporation, United States of America, 2015) and displayed in figures, tables and narratives. The association of CA risk factors with HIV status was assessed using Chi-square test and deemed significantly associated if $p < 0.05$. We also performed backward multivariate logistic regression analyses to examine the association between HIV status and various risks.

Results

The number of new CA patients in 5 years, from January 2016 to December 2020, was 115. There were 71 (61.7%) men and 44 (38.3%) women. The mean age of the patients in this study was 29 ± 9.90 years, with the youngest being 14 years old and the oldest 71 years old. The number of HIV-positive CA patients was 31 (27%), while the number of HIV-negative CA patients was 84 (73%) (Table 1). The location of the CA in men and women in this study is shown in Figure 1.

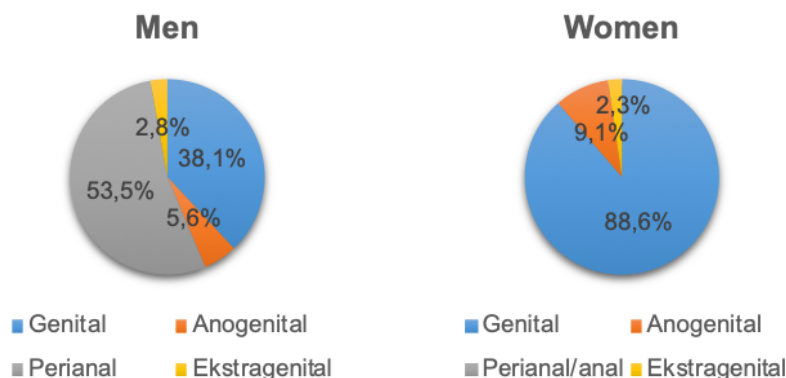


Figure 1. Percentage of lesion locations in men and women

Table 1. Sociodemographic characteristics, risk behavior, disease progression, and relationship with HIV in CA patients

| | n (N=115) | % | HIV (+) (N=31) | HIV (-) (N=84) | p-value |
|----------------------------|----------------------|----------|---------------------------|---------------------------|----------------|
| Age | | | | | |
| Mean ± SD | 29±9.89 | | | | |
| Median (min-max) | 27(14-71) | | | | |
| Age Group (year) | | | | | |
| 12-16 (early teens) | 1 | 0.9 | 1 (0.9%) | - | 0.121 |
| 17-25 (late teens) | 50 | 43.5 | 18 (15.7%) | 32 (27.8%) | |
| 26-35 (early adulthood) | 45 | 39.1 | 6 (5.2%) | 39(33.9%) | |
| 36-45 (late adulthood) | 10 | 8.7 | 3(2.6%) | 7 (6.1%) | |
| 46-55 (early elderly) | 6 | 5.2 | 2 (1.7%) | 4 (3.5%) | |
| 56-65 (late seniors) | 2 | 1.7 | 1 (0.9%) | 1 (0.9%) | |
| >65 (senior) | 1 | 0.9 | - | 1 (0.9%) | |
| Gender | | | | | |
| Man | 71 | 61.7 | 29 (25.2%) | 42 (36.5%) | 0.000 |
| Woman | 44 | 38.3 | 2 (1.8%) | 42 (36.5%) | |
| Marital status | | | | | |
| Married | 61 | 53 | 9 (7.8%) | 52 (45.2%) | 0.002 |
| Unmarried | 54 | 47 | 22 (19.2%) | 32 (27.8%) | |
| Sexual partners | | | | | |
| 1 Sexual partner | 54 | 47 | 3 (2.6%) | 51 (44.4%) | 0.000 |
| >1 sexual partner | 61 | 53 | 28 (24.3%) | 33 (28.7%) | |
| Sexual orientation | | | | | |
| Homosexual | 33 | 27.8 | 19 (16.5%) | 14 (12.2%) | 0.000 |
| Heterosexual | 72 | 63.5 | 4 (3.5%) | 68 (59.1%) | |
| Bisexual | 10 | 8.7 | 8 (7.0%) | 2 (1.7%) | |
| Sexual intercourse | | | | | |
| Genito-genital | 58 | 50.4 | 4 (3.5%) | 54 (47%) | 0.000 |
| Genito-anal | 18 | 15.7 | 13 (11.3%) | 5 (4.3%) | |
| Genito-oral-anal | 39 | 33.9 | 14 (12.2%) | 25 (21.7%) | |
| Location of lesions | | | | | |
| Genital | 66 | 57.4 | 3 (2.6%) | 63 (54.8%) | 0.000 |
| Perianal/anal | 38 | 33.0 | 24 (20.9%) | 14 (12.1%) | |
| Anogenital | 8 | 7 | 3 (2.6%) | 5 (4.3%) | |
| Extragenital | 3 | 2.6 | 1 (0.9%) | 2 (1.7%) | |
| Lesion shape | | | | | |
| Acuminata | 50 | 43.5 | 18 (15.7%) | 32 (27.8%) | 0.021 |
| Papules | 49 | 42.6 | 6 (5.2%) | 43 (37.4%) | |
| Flat | 7 | 6.1 | 3 (2.6%) | 4 (3.5%) | |
| Giant | 9 | 7.8 | 4 (3.5%) | 5 (4.3%) | |

The highest number of CA patients with HIV-positive status was 18 (15.7%) in the 17–25-year age group, and the highest number of CA patients with HIV-negative status was 39 (33.9%) in the 26–35-year age group. There was no significant relationship between the age group and CA

patients with HIV (p=0.121). The number of HIV-positive men were 29 (25.2%) patients, while HIV-positive women were 2 (1.8%) patients. In this study, there was a significant relationship between gender and CA patients with HIV, with a value of p<0.05 (p=0.000), and a significant relationship

between the number of sexual partners and CA patients with HIV ($p=0.000$). Bivariate analyses of marital status, sexual partner, sexual orientations, sexual intercourse, location, and lesion shape of CA with HIV status are shown in Table 1.

The multivariate logistic regression analyses showed that age, marital status, sexual partner, sexual orientation, and location of lesions were independent risk factors for HIV in CA patients. Age group with a value of $p<0.05$ ($p=0.000$) has a partial effect on HIV status in CA (RR 0.422; 95%CI 0.288,

0.619). Married patients had a lower risk of being HIV positive (RR 0.165; 95%CI 0.051, 0.538). Patients with more than one sexual partner had a higher risk for HIV positive (RR 1.681; 95%CI 0.487, 5.807) and homosexual had 5-fold increased risk (RR 5.294; 95%CI 1.583, 17.704). The location of the lesion with a value of $p<0.05$ ($p=0.033$) has a partial effect on HIV status in CA (RR 2.089; 95%CI 1.062, 4.107). Gender, sexual intercourse, and lesion shape did not have a significant effect in the multivariate analysis (Table 2).

Table 2. Multivariate logistic regression analyses of risk factors associated with HIV infection

| Variable | B | Relative Risk (RR) | 95%CI | p-value |
|---------------------|--------|--------------------|--------------|---------|
| Age | -0.862 | 0.422 | 0.288-0.619 | 0.000 |
| Gender | -0.962 | 0.337 | 0.51-2.245 | 0.261 |
| Marital status | -1.802 | 0.165 | 0.051-0.538 | 0.003 |
| Sexual partners | 0.520 | 1.681 | 0.487- 5.807 | 0.011 |
| Sexual orientation | 1.667 | 5.294 | 1.583-17.704 | 0.007 |
| Sexual intercourse | -0.251 | 0.778 | 0.479-1.262 | 0.309 |
| Location of lesions | 0.737 | 2.089 | 1.062-4.107 | 0.033 |
| Lesions shape | -0.150 | 0.861 | 0.494-1.498 | 0.596 |

B=Basic; RR=Relative risk; CI= confidence interval

In heterosexuals, 64 (88.8%) patients had genital lesions, and in homosexuals, 30 (90,9%) patients had perianal/anal lesions (Figure 2). In this study, out of 71 men, 28 (39.4%) were heterosexual, and 43 (60.6%) had sex with men (MSM). In Table 3, it is shown that there was a significant relationship

between MSM and HIV status ($p=0.000$; RR 21.938; 95%CI 8.79, 93.63). MSM were 22 times more likely to be HIV-positive CA than heterosexual men. In this study, 37 (86%) MSM had perianal/anal lesions, while 26 (92.8%) non-MSM had genital lesions (Figure 3).

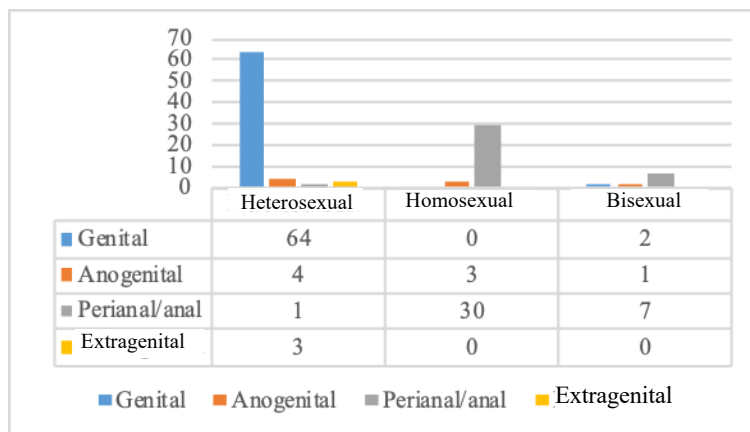


Figure 2. Bar chart comparison of lesion location with patient's sexual orientation

Table 3. MSM risk factors for HIV (+) in CA patients

| | HIV (+) (N=31) | HIV (-) (N=84) | Total (%) (N=115) | p-value | Relative Risk (RR); 95% CI |
|---------|-------------------|-------------------|----------------------|---------|-------------------------------|
| MSM | 27 (38%) | 16 (22.6%) | 43 (60.6%) | 0.000 | 21.938; |
| Non-MSM | 2 (2.8%) | 26 (36.6%) | 28 (39.4%) | | 8.790-93.63 |

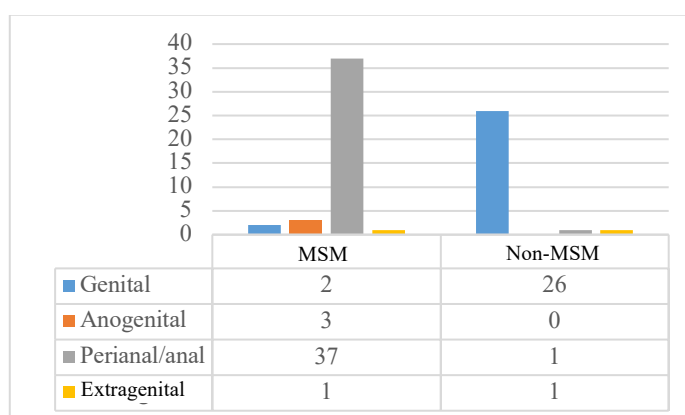


Figure 3. The number of MSM/non-MSM with lesion location in male CA patients.

Discussion

Condyloma acuminata (CA) is a sexually transmitted infection caused by human papillomaviruses (HPV).¹ Human papillomavirus is often asymptomatic and transient but can persist depending on the type of HPV and the host immune system.¹⁴ In immunocompromised patients, latent HPV infection can be controlled by cellular immunity, leading to lesion regression. In patients with HIV, CA lesions are slow to resolve and persistent with broad clinical features.¹²

HIV patients are more frequently co-infected with sexually transmitted diseases than those without HIV infection, with a greater incidence rate by 1.5-3 times.¹⁵ The incidence of CA in HIV infection is about 5% to 27%.¹⁶ This increased risk is not reduced by using antiretrovirals (ARVs). Human Papilloma Virus (HPV) may worsen with immune reconstitution syndrome. The pattern of spread of HIV in HPV infection is different from that in other STIs, because HPV has no significant impact on the inflammatory response of the genital area and is not associated with the shedding of HIV.¹⁵

HPV infection is increased in immunosuppressed patients such as HIV infection. The difficulty of viral clearance in immunosuppressed patients makes clinical manifestations longer or more persistent.^{3,12} In patients with HIV, there is a decrease in Langerhans cells, CD4+ T-cell lymphocytes, macrophages, neutrophils, and natural killer cells, causing changes in local immunity and an increase in HPV infection in tissues.^{6,14} CA are often asymptomatic and are not treated until they cause discomfort, pruritus, or bleeding. CA are found in groups at high risk of contracting HIV.¹⁷ The concentration of HIV in semen and vaginal fluids is

directly related to the number of leukocytes migrating to the genital tract.¹⁵

In this study, the number of HIV-positive CA patients was 31 (26.8%), while HIV-negative CA patients were 84 (73.2%). Among men with CA, 29 (93%) were HIV-positive, higher than that among women ($p= 0.000$). This study's results resemble the study by Puspawati et al.⁴ in 2018, which found that the number of CA patients with HIV positive was 58 (22.31%) and CA patients with HIV-negative were 202 (77.69%). Tobing et al.¹⁸ in 2020 found that 60% men and 40% women with CA were accompanied by HIV. Men have a high-risk behavior for CA infection with HIV as men are more sexually active and have more sexual partners than women. This makes it easier for men to spread sexually transmitted diseases and HIV than women.¹⁹

The number of HIV-positive status was 18 (58%) in the 17-25-year age group, the highest among all age groups. In this study, the age group contributed significantly ($p = 0.000$) in the multivariate analysis (Table 2). This study is in accordance with studies by Brown et al.²⁰ and Dhumale et al.⁵ Brown et al.²⁰ in 2018 found that 51.5% patients with CA in the 18-24 year age group were HIV positive. In the 15-30 year age group, the patients were more sexually active and had more than one sexual partner.²⁰ Dhumale et al.⁵ in 2017 found that 16 out of 25 patients with CA in the age group of 15-30 years were HIV-positive and stated that the age and HIV status of CA patients had a significant relationship.⁵ Condyloma acuminata decreases progressively with increasing age due to lower sexual activity in old age.²¹

In this study, all patients, both married and unmarried had sexual intercourse. Of the 31 HIV-positive CA patients, 22 (70.9%) were unmarried.

In 84 HIV-negative CA patients, 52 (61.9%) were married. In Table 2, marital status had a significant relationship with HIV-positive status ($p = 0.002$) and risk of suffering CA with HIV (RR 0.165; 95%CI 0.051, 0.538). The results were similar to that of Low et al.¹⁴ in 2011, which found that 38.5% HIV-positive CA patients were unmarried and 21.9% HIV-positive CA patients were married. Marital status had a significant relationship with CA cases with HIV ($p < 0.001$).¹⁴ Clanner-Engelshofen et al.²² in 2020 found that 50.2% of CA patients were single. In this study, unmarried patients tended to change partners, with men having more than one sexual partner and some having sex with men (MSM).

Based on this study, there is a significant relationship between incidence of CA with HIV and number of sexual partners (Table 2). The results of this study are similar of Dhumale et al. 2017, a significant relationship between the number of sexual partners and CA with HIV, 92% of CA patients with HIV have multiple sexual partners, while many HIV-negative CA patients have one sexual partner.⁵ Number of sexual partners > 1 or changing partners is a risk factor for infection with HPV, HIV, and other STIs.^{5,6,14}

In this study, the most common method of sexual intercourse was genito-genital in 58 (50.4%) patients, while 15.7% and 33.9% were genito-anal and genito-anal-oral, respectively. Genito-genital sexual intercourse was the most common in HIV-negative as many as 54 people (47%), while in HIV-positive the genito-anal-oral method of sexual intercourse was 14 people (12.2%). In this study, there was a significant relationship between sexual intercourse and cases of CA with HIV ($p = 0.000$). The study by Clanner-Engelshofen et al.²² in 2020 found that as many as 8.4% of CA patients have a relationship between anal penetration and CA. Tobing et al.¹⁸ in 2020 found the most location was perianal/anal as many as 60% patient. HPV can increase the transmission of HIV due to the inflammation and the increase in number of HIV target cells at the site of infection, depending on the sexual intercourse. Individuals who have receptive anal sex often have an anal CA.¹⁷

The most frequent location of the lesions in HIV-positive CA patients in this study was perianal/anal (20.9), while anogenital and genital were 2.6% and extragenital was 0.9%. In HIV-negative CA patients, 63 (55.8%) patients had genital lesions and 14 (12.1%) had perianal/anal lesions. There was a significant relationship between the location of CA lesions and HIV status ($p = 0.000$). The results of this study were similar to those of Dhumale et

al.⁵ in 2017, which found that CA is associated with HIV infection ($p < 0.01$). Extragenital CA lesions were common in HIV-positive patients and there was no difference in the distribution of CA lesions.⁵ Condyloma acuminata in males are found under the foreskin or on the shaft of the penis and in females on the genitals or introitus.¹⁷ The clinical manifestations of perianal or anal, oral, and pharyngeal lesions depend on the sexual intercourse.²²

Based on clinical importance, CA is divided into acuminate, papule, flat, and transitional forms associated with malignancy (giant Buschke-Lowenstein condyloma and bowenoid papulosis). In this study, 43.5%, 42.6%, 6.1%, and 7.8% were acuminate, popular, keratotic, and Giant's lesions, respectively. In HIV-positive CA patients, acuminate lesions and Giant condyloma were present in 18 (15.7%) and 4 (3.5%), respectively. The shape of the CA lesion had a significant relationship with HIV status ($p = 0.000$). The results of this study are similar to those of Oktaviyanti et al.²³ in 2018, which found that almost all CA lesions were acuminate in 283 patients (88.9%) and papules in 33 patients (10.4%). Condyloma acuminata can be widespread or diffuse due to autoinoculation or immunosuppression. HIV-positive lesions may be extragenital, persistent, and difficult to resolve because of the patient's immune defect.⁵ This HIV condition will also cause the development of CA lesions to be longer, easier to recur, and larger (giant condyloma).^{3,12}

In this study, of 31 HIV-positive CA patients, 19 (61.3%) were homosexual, 4 (12.9%) were heterosexual, and 8 (25.8%) were bisexual. There was a significant relationship between sexual orientation and patients. Condyloma acuminata with HIV positive ($p = 0.000$). The results of this study are similar to the study of Dhumale et al in 2017, that there is a significant relationship between CA with HIV positive and homosexuality ($p = 0.041$). Most CA and HIV-negative patients were heterosexual.⁵ In the study of Brandon et al in 2018 it was reported that CA with HIV positive was more prevalent in the homosexual group (54.2%).²⁰ Homosexuals or MSM groups are more likely to suffer from sexually transmitted diseases with HIV than heterosexuals.¹⁹

In this study, out of 71 men, 28 (39.4%) were heterosexual men, and 43 (60.6%) men had sex with men (MSM). In this study, there were 31 CA patients with HIV positive, most of whom were MSM as many as 27 people (87%). The MSM group was at risk of suffering from CA with HIV positive 22 times compared to heterosexual male

partners $p = 0.000$ and RR 21.938 (95% CI 8.79-93.63). The results same with Brandon et al in 2018, from 571 MSM and transgender people who were followed up for 2 years as many as 73 people (12.8%) suffered CA with HIV with an average incidence of as much as 6%.²⁰ Homosexuality or MSM is a risk factor for the spread of HIV in CA patients.¹²

In this study, 37 of 43 MSM had perianal/anal lesions, while 26 of 28 non-MSM had genital lesions. Anal manifestations are more common in males than females, with the highest prevalence in homosexual and bisexual males. A study by Clanner-Engelshofen et al.²² in 2020 found that perianal and anal CA were most common in young men who had sex with men. In the MSM group, there was an increase in cases of CA along with HIV infection. Men who have sex with men are at risk of developing anal CA, although the prevalence of anal CA in heterosexual men is also high.^{12,17} The MSM group can suffer from persistent HPV-16 infection in the anus for up to 6 months.¹²

This study has several limitations in data and standardization of medical records. The sample size is small and not homogeneous. Extracting complete data was difficult because some supporting data such as CD4+ levels, age at first sexual intercourse, sexual partner(s), time of HIV infection, and time of CA infection were not available in medical records. We suggest standardization of medical records for complete research data. Further research are needed with more subjects, homogeneous sample, and a case-control, cross-sectional, or cohort prospective study design to achieve complete dataset.

Conclusion

The prevalence of HIV-positive status in CA patients was 26.8% (31 out of 115 patients) in this study. Risk factors for HIV in CA that were significantly related in this study included gender, marital status, number of sexual partners, sexual orientation, sexual intercourse, location, and shape of lesions. Men have a 14-times higher risk of suffering HIV in CA. Having more than one sexual partner has a higher risk of contracting HIV in CA than having one sexual partner.

Acknowledgments

The author would like to thank the Faculty of Medicine, Universitas Sriwijaya. for providing this outstanding research opportunity.

Author Contributions

All authors act as guarantors of the manuscript. All authors contributed to the study design, data acquisition, chart abstraction, data analysis/interpretation, and manuscript drafting.

Conflict of Interest

The author declares that there is no conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or non-profit sectors.

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