HHS Public Access

Author manuscript

Lancet Reg Health Am. Author manuscript; available in PMC 2023 February 02.

Published in final edited form as:

Lancet Reg Health Am. 2023 January ; 17: . doi:10.1016/j.lana.2022.100382.

Development of a multivariable prediction model for anal high-grade squamous intraepithelial lesions in persons living with HIV in Puerto Rico: a cross-sectional study

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Declaration of interests

MSS reports support from NCI grants and from the AACR (2021 Faculty Scholar Award Minority and Serving Institution) to attend a conference meeting.

ES declare no competing interests.

TVR declare support from an NCI grant.

LP declare no competing interests.

JRC reports support from an NCI grant.

AAD declare no competing interests.

MT declare no competing interests.

APO reports support from NCI grants and contracts with Merck, outside the submitted work.

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Summary

Background—Persons living with HIV (PLWH) are at high risk of developing anal high-grade squamous intraepithelial lesions (HSIL). We aimed to develop a prediction model for anal HSIL based on individual characteristics of PLWH.

Methods—Cross-sectional study of PLWH aged ≥21 years who attended the Anal Neoplasia Clinic of the University of Puerto Rico Comprehensive Cancer Center from 2016 to 2022. The primary outcome was biopsy-confirmed anal HSIL. For each sex, relations between potential predictors and HSIL were examined using univariate (ULRM) and multivariable (MLRM) logistic regression models. Risk modelling was performed with MLRM and validated with bootstrapping techniques. The area under the ROC Curves (AUC) was estimated with 95% CI.

Findings—HSIL was detected among 45.11% of patients, 68.48% were males, and 59.42% were ≥45 aged. Multivariable analysis showed that, in women, the only significant predictor for HSIL was having a previous abnormal anal cytology ($p = 0.01$). In men, significant predictors for HSIL were having a previous abnormal anal cytology ($p < 0.001$) and a history of infection with any gonorrhoea ($p = 0.002$). Other suggestive predictors for HSIL among women were obesity and smoking. No association between smoking and HSIL among men was observed ($p < 0.05$). The AUC estimated among women (0.732, 95% CI: 0.651–0.811) was higher than in men (0.689, 95% CI: 0.629–0.748).

Interpretation—Our results support that the inclusion of individual characteristics into the prediction model will adequately predict the presence of HSIL in PLWH.

Funding—This work was supported by the NCI (Grants #U54CA096297, #R25CA240120), the NIGMS (Grant #U54GM133807), and the NIMHD (Grant #U54MD007587).

Keywords

Hispanics; Persons living with HIV; Anal HSIL; Early detection; Prediction model

Introduction

The incidence of squamous cell carcinoma of the anus (SCCA) is more than 30-fold higher in persons living with HIV (PLWH) compared to the general population.[1] Also, men who have sex with men (MSM) living with HIV exhibit an 80-fold higher risk of developing SCCA.[2] Around 90% of SCCA has been associated with persistent infection with high-risk human papillomavirus (HR-HPV), which PLWH are at higher risk for contracting.[3] Moreover, Puerto Rico (PR), one of the jurisdictions within the United States of America

(US), has a higher incidence (11.9 per 100,000 population) of HIV than other US states and territories and ranks 10th in the highest number of AIDS cases in the US.[4] Similar to the studies conducted in the continental US, SCCA risk among PLWH living in PR is greater than in the general population.[5] Previous studies have also reported evidence of anal cancer disparities between Puerto Ricans and Hispanics in the US. For example, Puerto Rican young men showed a 20% higher incidence of anal cancer than US Hispanics,[6] and after only three years of a diagnosis, men in PR have lower relative survival estimates than white men in the US.[7]

Greater risk of acquisition and persistence of HR-HPV infection makes PLWH vulnerable to the development of anal squamous intraepithelial lesions (SILs), and specifically anal high-grade intraepithelial lesions (HSIL), a necessary precursor for SCCA.[8,9] HR-HPV infection is less likely to clear spontaneously in immunocompromised patients, leading to even higher risks of developing physical symptoms and the progression of these lesions.[9] Furthermore, previous evidence suggests that HR-HPV infection, such as HPV-16, is implicated in nearly 90% of anal cancer cases.[10,11] All these factors have made anal cancer an increasingly concerning but preventable malignancy. Other risk factors for anal cancer include immunosuppression due to solid-organ transplantation, history of vulvar or cervical HSIL or cancer, history of receptive anal intercourse, history of genital warts, anal fissures or fistulas and smoking.[12]

Anal cancer behaves very similarly to cervical cancer: both are elevated among PLWH, have pathophysiological similarities, have a strong association with persistent HR-HPV infection, and are preceded by HSIL.[9] Although there is an ongoing debate among researchers regarding the potential benefits of screening for anal cancer and no evidence-based screening strategies for this disease exist, some experts recommend using anal cytology as primary screening followed by a high-resolution anoscopy (HRA) with biopsy in a high-risk populations such as PLWH, MSM, immunosuppressed people and women with a history of gynecologic HPV-related HSIL and cancer.[9,13,14] Other alternatives involve digital anorectal examination (DARE) to detect SCCA early.[8,15] Nevertheless, anal cytology has exhibited problems in terms of sensitivity and underestimation of lesion grade,[8,10] where most patients without HSIL will be referred for HRA, representing a significant burden for the patients and the health care system. Secondary prevention of anal cancer involves detecting and treating potentially precancerous lesions, like cervical cancer.[9]

Recently, the ANCHOR clinical trial informed that treating anal HSIL significantly reduces the risk of progression to anal cancer among PLWH.[12] Despite the knowledge of anal HSIL treatment efficacy, there are limited resources for HRA in most US states and jurisdictions given its costs and reduced availability of well-trained clinicians to perform this procedure.[12] Thus, current priorities include to identify optimal screening algorithms sufficiently sensitive and specific to identify anal HSIL. In PR, there are only four clinicians trained by the International Anal Neoplasia Society (IANS) to perform HRA.[10,16] Given the higher burden of HIV and anal cancer in PR, there is a need to identify those HIV patients at the highest risk of anal cancer that could benefit from anal cancer screening and treatment of precancerous lesions.

Risk prediction models combining individual patient factors (e.g., clinical and lifestyle risk factors and demographic characteristics) can categorize patients according to their risk for developing a measured outcome.[17] Risk prediction models have been developed for multiple diseases, such as cancer and chronic diseases.[17-21] However, literature on risk prediction models for anal HSIL, a precursor of anal cancer, based on individual and clinical characteristics is limited. We aim to develop a prediction model based on individual and clinical risk factors for detecting anal HSIL in PLWH using the steps recommended by Steyerberg and Vergouwe (2014).[22] This risk assessment tool aims to identify PLWH at the highest risk of anal HSIL and who need further management. We hypothesize that if we identify individual and clinical risk factors that predict the presence of anal HSIL among PLWH, people with these factors could benefit from anal cancer screening.

Methods

Source of data

Using a cross-sectional study, we performed secondary data analysis of patients who underwent anal cancer screening at the Anal Neoplasia Clinic (ANC) of the University of Puerto Rico Comprehensive Cancer Center (UPRCCC). Patients were referred from community-based clinics for further evaluation and management. The ANC provides services to patients from all over PR and specializes in the diagnosis of anal lesions and their treatment. Patients are referred if they have a previous abnormal anal cytology, are at risk of anal cancer, have symptoms that might suggest anal cancer, or have health concerns about anal cancer.[10] The ANC possesses the necessary equipment and personnel to perform anal cytology and HR-HPV testing, DARE, HRA, and HRA-directed anal biopsies, and remove anal lesions using electrocautery and infrared coagulation. In addition, the ANC is the first and only clinic in PR to offer HRA from physicians trained at the national level, including the only physician who specializes in both SCCA screening and treatment.[10] The ANC is located in San Juan, Puerto Rico, and is part of the National Cancer Institute-sponsored AIDS Malignancy Consortium (grant # UM1CA121947).

Participants

From May 10, 2016 to June 22, 2022, a total of 802 patients had been seen in the ANC. Most of these patients were PLWH (n = 552, 68.8%). Those PLWH examined for anal cancer and with a biopsy-confirmed result from the HRA were included in this secondary data analysis (n = 552, 100%). The Institutional Review Board of the UPRCCC approved this study.

Outcome

The primary outcome was the result of biopsy-confirmed anal HSIL (normal/LSIL vs. HSIL) as documented in the patient chart. A complete physical examination and an anal biopsy through HRA were obtained at the ANC's first visit and sent to a histopathology laboratory. The results were classified according to the LAST Project. According to the LAST Project, a person was diagnosed with anal HSIL if the biopsy found was classified as AIN3 or AIN2 with p16 staining positive.

Predictors

Predictors included demographics, clinical, and behavioural risk factors as reported by the patient at the first visit and documented in the patient chart. Demographic characteristics included age in years (<45 vs. ≥45), sex at birth (female vs. male), and marital status (partnered vs. single). Clinical factors included years living with HIV (<5, 5–9, 10–14, ≥15), last reported HIV viral load count (undetectable vs. detectable), Nadir CD4 count (cells/μl; ≥200 vs. <200), history of HPV vaccination (received one or more doses; yes vs. no), history of abnormal anal cytology (abnormal vs. normal), and having HR-HPV infection using the Cobas 4800 test through a 12 HR-HPV panel (16, 18 and other [31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68]; yes vs. no), and clinic measured body mass index (BMI, kg/m^2; underweight/normal vs. overweight/obese). Self-reported behavioural risk factors included age at first sexual intercourse (≤15, 16–18, ≥19 years), lifetime number of sexual partners (1–5 partners vs. ≥6 partners), sexual risk group (men sex with women, men sex with men, and women), history of lifetime anal sex type (insertive vs. receptive/both), history of infection with any gonorrhoea (yes vs. no), and current smoking (yes vs. no) as documented in the patient chart. Current smoking (yes vs. no) was defined considering three distinctive variables: history of lifetime smoking (yes vs. no), smoking at least 100 cigarettes in the entire life (yes vs. no), history of smoking in the last 12 months (yes vs. no), and currently smoked cigarettes (every day, some days, or not at all). The category of NO in the variable current smoking grouped those who reported: 1) not having smoked once in the entire life, 2) not having smoked 100 cigarettes in the entire life, 3) not having smoked during the past 12 months, or 4) currently smoked cigarettes-not at all. Meanwhile, the category of YES grouped those who reported: 1) currently smoked cigarettes-some days or every day.

Missing data

Given the high number of potential predictors (previous anal cytology, BMI, current smoking, age at first sexual intercourse, and the number of lifetime sex partners) with missing information, we performed multiple imputation analysis (MIA) to evaluate the potential bias of missing data in the multivariable prediction model for each sex. Multivariable imputation by chained equations (MICE), assuming data missing at random (MAR), was performed with ten imputations for each missing data. The missing values were imputed using the observed values of the following variables: the result of anal histology, sex at birth, age at visit, HR-HPV (any type) result, and history of any gonorrhoea (only considered as an additional variable for the males' model). The imputation method was run with the command *mi* in STATA, which uses the Rubin approach.[23]

Statistical analysis methods

Descriptive statistics were employed to characterize the study population. For each sex, tests of independence, using the Chi-square distribution were applied to examine the bivariate statistical associations between the different characteristics and anal HSIL. Additionally, for each sex, univariate logistic regression models (ULRM) and multivariate logistic regression models (MLRM) were used to assess predictors of anal HSIL. The inclusion criteria for the MLRM were to meet at least two of the following conditions: (1) known risk factors for anal HSIL according to the scientific literature, (2) p-values < 0.25 in the ULRM, or (3)

lower Bayesian Information Criteria (BIC) and Akaike Information Criterion (AIC) values. A Likelihood ratio test was performed to identify significant interaction terms in the MLRM. To assess the consistency of the MLRM, we applied cross-validation and bootstrapping (1000 replications) using the training sample (n = 132 for females and n = 334 for males). Afterwards, we performed an external validation using the participants recently evaluated at the Anal Neoplasia Clinic from August 3, 2021, to June 30, 2022 (n = 42 for females and n = 44 for males), as suggested by Steyerberg & Vergouwe. Finally, we merged the initial data with the external data to report the final results, due to adequate results in the external validation. The probabilities for predicting anal HSIL from the MLRM were categorized into five groups, using quintiles as cut-off points. The sum of these probabilities indicates the expected number of PLWH with anal HSIL. Afterwards, to characterize model performance in both samples, the ROC curves (AUC) were estimated. The optimal cut-point for referral was determined using the Youden statistic. Overall, the data analyses were performed with Stata 17 (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC.).

Role of the funding source—The funders had no role in study design, data collection, data analysis, interpretation, writing of the report, or the decision to submit.

Results

Participants

Table 1 shows the study participants' demographic, clinical, and risk behaviours' characteristics. Most study participants were males (68.48%), median age was 46.5 years, 87.14% had not been vaccinated for HPV, 76.99% had a previous abnormal anal cytology (ASCUS or worse), 72.64% reported having both receptive and combination of receptive/insertive anal sex, and 74.09% reported having six or more sex partners in their lifetime. Prevalence of biopsy-confirmed anal normal/LSIL among PLWH was 54.89% and for anal HSIL was 45.11%. Prevalence of any anal HR-HPV infection was 36.78%, 14.31% for HPV-16, and 5.80% for HPV-18 (data not shown).

The prevalence of specific characteristics and risk factors differed by sex (data not shown). More females were aged ≥45 years (73.68% vs. 54.85%) and overweight/obese (78.29% vs. 62.12%) as compared to males ($p < 0.0001$). Among high-risk sexual behaviours, having six or more sex partners in their lifetime (86.67% vs. 46.05%) was significantly higher in males than females ($p < 0.0001$). However, having the first sexual intercourse at 15 years or less (43.42% vs. 37.27%) was slightly higher in females than males ($p = 0.06$). The prevalence of a history of infection with any gonorrhoea was significantly higher among males than females (16.36% vs. 4.61%, $p < 0.0001$). No differences were found in the prevalence of anal HR-HPV infection by sex (34.87% in females vs. 37.27% in males, $p = 0.61$). Lastly, the prevalence of biopsy-confirmed anal HSIL was higher among males than among females (47.62% vs. 39.66%, $p = 0.08$).

Model development and specification

The evaluation of the magnitude of association between potential predictors and biopsy-confirmed anal HSIL was stratified by sex. In females, based on the ULRM, having anal HSIL was associated ($p < 0.25$) with previous abnormal anal cytology, anal infection with HR-HPV (any type), age at first sexual intercourse, lifetime number of sex partners, and current smoking (Table 2) were included in the MLRM. Other predictors such as age and BMI were not associated ($p > 0.25$) with having anal HSIL among females according to the ULRM but were included in the MLRM due to their significance in scientific literature.[24,25] We evaluated interaction in the MLRM. Since the interaction terms between age at visit with HR-HPV infection, lifetime number of sexual partners, and age at first sexual intercourse were significant ($p < 0.05$), these terms were included in our final model. The final MLRM for females included age, previous abnormal anal cytology, BMI, current smoking, anal infection with HR-HPV (any type), age at first sexual intercourse, lifetime number of sex partners, and interaction terms previously described. The only predictor that reached statistical significance ($p < 0.05$) in the MLRM was previous abnormal anal cytology. Women living with HIV who had a previous abnormal anal cytology were more likely to have anal HSIL (OR: 5.63, 95% CI: 1.50–21.15) than those with a previous normal anal cytology. Women living with HIV with HR-HPV infection were more likely to have anal HSIL (OR: 3.45, 95% CI: 0.80–14.82) than those without HR-HPV infection. Moreover, women living with HIV who were overweight/obese (OR: 2.31, 95% CI: 0.88–6.06) and those who were current smokers (OR: 1.91, 95% CI: 0.84–4.39) had higher odds of having anal HSIL than their counterparts; while the magnitude of these findings was strong, these results were not statistically significant. There were no differences in the estimated adjusted ORs in the case-complete analysis versus imputation analysis (Table 2).

Among males, based on the ULRM, having anal HSIL was associated ($p < 0.25$) with previous abnormal anal cytology, anal infection with HR-HPV (any type), BMI, age at first sexual intercourse, and history of infection with any gonorrhoea (Table 3) were included in the MLRM. Other predictors such as age, current smoking, and lifetime number of sex partners were not associated ($p > 0.25$) with having anal HSIL among males according to the ULRM but were included in the MLRM due to their significance in scientific literature. We evaluated interaction in the MLRM, and no significant interaction terms were found in the MLRM in males ($p > 0.05$). The final MLRM for males included age, previous abnormal anal cytology, BMI, current smoking, anal infection with HR-HPV (any type), age at first sexual intercourse, lifetime number of sex partners, and history of infection with any gonorrhoea. The predictors that reached statistical significance ($p < 0.05$) in the MLRM were previous abnormal anal cytology and history of infection with any gonorrhoea. Men living with HIV who had a previous abnormal anal cytology were more likely to have anal HSIL (OR: 3.78, 95% CI: 2.08–6.88) than those with a previous normal anal cytology. Moreover, men living with HIV who reported a history of infection with any gonorrhoea had higher odds of having anal HSIL (OR: 2.79, 95% CI: 1.48–5.25) than those without history of infection with any gonorrhoea. However, men living with HIV who are overweight/obese had lower odds of having anal HSIL (OR: 0.73, 95% CI: 0.45–1.17) than those who are underweight/normal; this finding was not statistically significant. No association was found between current smoking and anal HSIL in men living with HIV. There were no differences

in the estimated adjusted ORs in the case complete analysis versus imputation analysis (Table 3).

Model performance

Among women living with HIV, the estimated AUC for anal HSIL based on our prediction model was 0.732 (95% normal-approximation CI: 0.654–0.809) (Fig. 1). Thus, the prediction model has a 73% probability of correctly distinguishing women having or not having anal HSIL. In this group, the optimal cut-point to discriminate between having or not having anal HSIL, based on the Youden statistics, was when the probabilities of being diagnosed with anal HSIL were greater than 22%; as a consequence, under this cut-off point, the number of referrals to further management decreased from 100% to 59% (Table 4). The p-value of the Calibration belt and test for internal validation indicates no statistical difference (p = 0.653) between model predictions and the 45-grade line (perfect calibration) (Fig. 2).

Among males living with HIV, the estimated AUC for anal HSIL, based on our prediction model, was 0.689 (95% normal-approximation CI: 0.629–0.748) (Fig. 3). Thus, the prediction model has a 68.9% probability of correctly distinguishing men having or not having anal HSIL. In this group, the optimal cut-point to discriminate between having or not having anal HSIL, based on the Youden statistics, was when the probabilities of being diagnosed with HSIL were greater than 37%; as a consequence, under this cut-off point, the number of referrals to further management decreased from 100% to 59% (Table 5). The p-value of the Calibration belt and test for internal validation indicates no statistical difference (p = 0.349) between model predictions and the 45-grade line (perfect calibration) (Fig. 4).

Lastly, MIA was used to evaluate the potential bias of missing information in our prediction model stratified by sex (data not shown). When we compared the estimated AUC through MIA (0.710 in females and 0.676 in males) with the estimated AUC in the complete-case analysis (0.732 in females and 0.689 in males), this suggests that there is no information bias in the prediction capacity of our prediction model due to missing information.

Discussion

Despite there being no definitive approach to managing anal HSIL, evidence suggests that treating anal HSIL among PLWH can significantly reduce the risk of progression to anal cancer.[12,26] Given the limited resources available in PR, a US territory, to diagnose and treat anal HSIL and the low sensitivity of anal pap tests,[9] we need to strengthen our capacity to accurately identify PLWH at the highest risk of anal HSIL and who need further diagnostic tests. Using a multivariable logistic regression model, we built a predictive model for anal HSIL, by sex, based on demographic, clinical, and anal cancer risk factors in PLWH in PR. We found sex differences in the performance of the prediction model for anal HSIL among PLWH. The AUC estimated among women (AUC = 0.732, 95% CI: 0.651–0.811) was higher than in men (0.689, 95% CI: 0.629–0.748). Despite this difference, the AUC estimated among men living with HIV is close to the optimum acceptable value of 0.70 or more.[17] Our study population was high-risk, as 45.11% of patients had biopsy-confirmed

anal HSIL. This result is high compared to what has been previously reported in other clinic-based populations.[27-29]

Compared with studies of anal HPV infection, studies aimed to develop a prediction model for anal HSIL among PLWH based on demographics, clinical, and lifestyle characteristics are extremely limited. We found one prospective study aimed to detect and predict anal HSIL among HIV-positive and HIV-negative men who have sex with men (MSM) using biomarkers such as high-risk HPV DNA genotyping, HPV E6/E7 mRNA, and p16 immunocytochemistry,[30] instead of individual characteristics. They found that E6/E7 mRNA had the highest sensitivity (64.7%, AUC = 0.61) and correctly classified the highest number of prevalent HSIL cases. However, the AUC estimated by our prediction model based on individual characteristics among men and women living with HIV is higher than the AUC obtained by the previous study using biomarkers for HSIL. Others have reported prediction models for other malignancies based on individuals' characteristics including colorectal cancers and cervical cancer. For example, Li et al. developed a prediction model for colorectal cancer in a Tianjin community based on individual characteristics and obtained an AUC of 84% (95% CI: 82%–86%) when demographics and clinical characteristics with fecal immunochemical test (FIT) were used, followed by 76% (95% CI: 74%–79%) for FIT alone, and 73% (95% CI: 71%–76%) for the demographics and clinical characteristics alone.[31] Rothberg et al. developed a prediction model for cervical intraepithelial neoplasia grade 2 or higher (CIN2+) lesions based on demographic factors and medical history using data from 33 primary care practices in the United States.[21] They found that the model based on HPV status and demographics has an AUC of 0.81, 0.72 for HPV alone and 0.71 for demographics alone. Thus, these studies demonstrate that it is possible to develop prediction models to identify high-risk individuals based on information (e.g., individual characteristics) available at a baseline clinical visit.

Our multivariable regression analysis showed that, in women living with HIV, the only statistically significant predictor for anal HSIL was a previous abnormal anal cytology ($p < 0.05$). However, the AIDS Malignancy Consortium 084 study has reported that the strongest predictors for anal HSIL among women living with HIV are lower current CD4 T-cell counts and a history of anal intercourse.[27] Our data also showed that in men living with HIV, the only two statistically significant predictors for anal HSIL were having a previous abnormal anal cytology and having a history of infection with any gonorrhoea ($p < 0.05$). The association of anal HSIL with having a previous abnormal anal cytology was previously reported among men living with HIV in an urban black population.[32] The observed significant association between anal HSIL and history of infection with any gonorrhoea in our data was surprising. However, studies have reported that sexually transmitted infections (STIs) such as chlamydia and gonorrhoea increased the risk of anal squamous intraepithelial lesions[28] and anal cancer.[33] Moreover, McCloskey et al. reported that the seropositivity for HIV, HSV-2, *T. pallidum*, HBV, and HCV and history of gonorrhoea or chlamydia exert a powerful amplifying factor increasing the risk of anal HSIL above the risk of HR-HPV infection alone in both HIV-positive and HIV-negative patients.[34] While the association of HR-HPV infection and anal HSIL was marginally significant for both men and women living with HIV in our study ($p > 0.05$), others have reported a significant association between these variables, but when the HPV genotype has been considered, the fraction of

anal cancer attributable to HPV-16 is smaller in the HPV-positive population.[35] Moreover, anal warts were associated with anal HSIL,[36] however, we didn't found an association between history of genital warts and anal HSIL in our study, which may due to the small number of patients who reported a history of genital warts (54 [9.8%] of 552 patients) or maybe because to they were unaware of the presence of genital warts. Given the high prevalence of HR-HPV infection in the study population and the relevance of HR-HPV infection as a potential biomarker for HSIL,[9] future studies should also evaluate the development of prediction models in persons positive for HR-HPV infection. Also, findings support that further studies should assess the clinical association between anal HSIL and other STIs such as gonorrhoea, including the syndemic synergy interactions and potential biological mechanisms between infection with gonorrhoea, HIV, and HR-HPV.

Although results were not statistically significant ($p > 0.05$), other suggestive predictors for anal HSIL among women living with HIV according to our multivariable analysis were obesity and smoking. In our study, obese women had increased odds of HSIL and obese men had decreased odds of HSIL. Limited information is available regarding the association between anal HSIL and obesity. However, obesity has been associated with the development of cancer, including cervical cancer.[37] Due to the suggestive association between anal HSIL and obesity and given the similarity in the pathophysiology of anal cancer with cervical cancer and the role of chronic inflammation in the development of certain cancers, future studies should assess the association between obesity and anal HSIL.[37] The association between smoking and anal HSIL was previously well-documented.[27,33] However, in our study no association was observed between smoking and anal HSIL among men living with HIV ($p > 0.05$). A recent study using data from the ANC reported a significant association between current smoking and anal HSIL after adjusting by age, sexual risk group, HIV status, lifetime number of sexual partners, and anal HR-HPV infection.[33] While the prevalence of current smoking (25.18%) was high in our study population, the null association between smoking and anal HSIL in our study was surprising and may be due to the limitation of the data collected in the ANC to properly evaluate frequency and amount of smoking (to distinguish between those with higher versus lower tobacco consumption) or maybe due to social desirability inherent in patient interviews studies which could have caused biased reporting of this behaviour. A previous study among HIV-positive men and women 18 years and older receiving HIV care in PR reported a similar prevalence of current cigarette use (29.0%) and daily smoking was reported in 76.7% of them.[38] Further studies should assess robust smoking indicators to understand better the impact of smoking, including frequency and number of cigarettes, on anal HSIL among HIV-positive patients.

Anal HR-HPV infection, early sexual initiation (<19 years), and having six or more sexual partners are other suggestive predictors for anal HSIL in both men and women living with HIV according to our multivariable model. Similar findings for the importance of these factors were found in previous studies of anal HSIL and anal cancer in PWLH,[3,8,10,11] which strengthened their inclusion in the MLRM. Previous findings support our hypothesis that the inclusion of individual and high-risk behaviours into the prediction model will predict the presence of anal HSIL in PLWH. Beyond the scope of our study, our results show a greater need for public health promotion targeted towards PLWH, for which this model could be used to selects high-risk patients for intervention therapy.

The size limitation of the final sample included in the multivariable model due to missingness did not significantly impact the prediction capacity of our models by sex. Nonetheless, the reduced sample size limited our ability to stratify analysis between MSM and heterosexual men, and by HPV status; for which risk factors and thus the variables relevant for the prediction model could be different.[39] Despite this, our models reached close-to-acceptable discriminatory capacity in both men and women. This could signify that factors that are primarily self-reported measures are not entirely sufficient but could be complementary to more robust predictors. Previous studies have considered predictors, such as socioeconomic factors (e.g., employment) and clinically confirmed factors, such as HIV RNA level, CD4 count, Nadir CD4 count, and years living with viral suppression,[11,25] which we did not have access to or were incomplete. Furthermore, the addition of disease biomarkers could develop a more robust model with markers, such as HPV-related viral load markers, E6/E7 mRNA expression, and dual cytology staining of p16INK 4a/Ki 67 antibodies in combination with HPV genotyping and persistence.[26,40] Lastly, the inclusion of imputation methods in our study showcases how imputation could be valuable for corroborating findings of prediction models when substantial amounts of missing data are present.

Limitations

Our study has several limitations to be considered. First, our prediction model was developed using data from the only clinic in PR that offer HRA from trained physicians. Therefore, we were not able to use a larger cohort for external validation. Second, most individual factors were self-reported and subject to recall bias and social desirability (e.g., anal sex, age at first sexual intercourse, and the number of lifetime sex partners), thus could have suffered from under-reporting. Third, the present study was limited to the population of PLWH referred to the ANC in PR, limiting the study's generalizability. The population referred to the ANC is usually symptomatic or has a history of abnormal anal cytology, thus information from asymptomatic patients or those without a history of abnormal anal cytology is not available. Fourth, the model did not consider important biomarkers for anal cancer, as the database is built upon self-reported data at baseline visits from patients who visit the ANC. Fifth, while the study population is mostly of Hispanic origin, ethnicity was not collected in the patient chart, limiting our capacity to perform an ethnicity-specific analysis. Sixth, clinically informed factors, such as CD4 counts, viral HIV load, genital warts and confirmed clinical history of STDs, instead of self-reported data, could improve future prognostic models as these factors have been considered in previous research.[11,21] Lastly, HPV vaccination, which has been associated to prevent persistent HPV infection among PLWH,[41] could not be considered in our prediction model given that only 7.1% of the sample reported being vaccinated. Nonetheless, our results point us in a promising direction. The addition of imputation methods allowed us to approximate and understand that neither sample size nor the amount of missing data for specific variables were crucial in our prediction capacity. And as previously mentioned, this is, to our knowledge, the first study of this type focused on Puerto Rican PLWH, which could set the basis for future attempts at more robust models.

Conclusions

Despite most HPV infections being transient, PLWH are at higher risk of persistent HR-HPV infection due to their immunodeficiencies, which could lead to the development of anal cancer.[8,9] Thus, estimating the risk of anal HSIL, the precursor lesion for anal cancer, among PLWH may help clinicians identify high-risk sub-groups for intervention therapy to reduce their risk of anal cancer after anal HSIL detection. Further studies focusing on individual risk factors are needed to improve the predictive capacity of a prediction model for anal HSIL, which remains a promising area. Additionally, future studies could focus on developing a clinical decision support system (e.g., a free App) to be used in the clinical setting to allow a personalized risk assessment of anal HSIL among PLWH based on individual and clinical factors. Targeted screening for anal cancer could potentially benefit from the identification of individual risk factors that can be used to identify a high-risk sub-group among PLWH, such as those with persistent HPV infections, those who received recent treatment for pre-cancerous lesions, and those who have not been vaccinated nor recently screened, which avoids over screening and over referral of PLWH at low risk for SCCA. Targeted screening for anal HSIL is extremely important given that there are limited resources globally (e.g., HRA technology and well-trained physicians in HRA) for screening and treating pre-cancerous anal lesions. This data could then expand translational studies to inform future strategies to optimize current anal cancer screening strategies, potentially adapting to Hispanics in the US and other populations worldwide.

Acknowledgements

The research reported in this publication was supported by Award Grant Number #3U54CA096297-17S1 and #5R25CA240120-02 from the National Cancer Institute of the National Institutes of Health, and by The Hispanic Alliance for Clinical and Translational Research grant support (Award Number #U54GM133807 from the National Institute of General Medical Sciences and #2U54MD007587 from the National Institute on Minority Health and Health Disparities). The following content is the authors' sole responsibility and does not necessarily represent the official views of the National Institutes of Health.

Data sharing statement

We will make aggregated, non-identified data and associated documentation available to any academic institution that requests them after analyses are completed and significant findings are reported through publication in peer-reviewed journals. We will provide these resources under a data-sharing agreement that provides for (1) a commitment to using the data only for research purposes; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed.

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Research in context

Evidence before this study

We searched PubMed with no language restrictions for publications reporting the development and validation of a prediction model for anal HSIL based on individual patient factors among persons living with HIV (PLWH). We used the search terms ("anal HSIL" OR "anal high grade squamous intraepithelial lesions") AND ("risk prediction" OR "risk assessment" OR "risk modeling" OR "prediction model") AND ("persons living with HIV" OR "HIV-positive") AND ("model development" OR "model validation"). The search was directed to manuscripts focused on adults aged 19+ years living with HIV, published between January 1, 2012, and July 13, 2022. Eleven publications were identified. None of the publications aimed to develop a prediction model for anal HSIL among PLWH based on individual patient factors. Only one prospective study aimed to detect and predict anal HSIL among HIV-positive and HIV-negative men who have sex with men (MSM) using biomarkers such as high-risk HPV DNA genotyping, HPV E6/E7 mRNA, and p16 immunocytochemistry, instead of individual patient factors. They found that E6/E7 mRNA had the highest sensitivity (64.7%) and correctly classified the highest number of prevalent HSIL cases.

Added value of this study

To our knowledge, this study is the first to evaluate the feasibility of developing a prediction model for detecting anal HSIL in PLWH based on individual patient factors, stratified by sex and focused on PLWH in Puerto Rico. We have included data from 552 PLWH who had been seen in the only clinic in Puerto Rico specialized in diagnosing and treating anal lesions. We propose a prediction model of anal HSIL, including information available at the baseline clinical visit on demographics, clinical, and behavioral risk factors. We observed sex differences in the predictors for anal HSIL among PLWH. A history of abnormal anal cytology was the strongest predictor for anal HSIL in men and women living with HIV. However, our data revealed that in men living with HIV, having a history of infection with any gonorrhea is another strong predictor of anal HSIL. Our findings support our hypothesis that the inclusion of individual patient characteristics could predict the presence of anal HSIL in PLWH.

Implications of all the available evidence

Even though this is a cross-sectional study, it supports further development of risk assessment tools for anal HSIL, based on individual patient characteristics, to be used as a community-based anal HSIL screening tool on PLWH. In clinical practice, predicting whether or not a patient will develop an anal HSIL will enable us to protect the limited resources within the health care system and to refer for further evaluation only those patients at the highest risk of developing anal cancer.

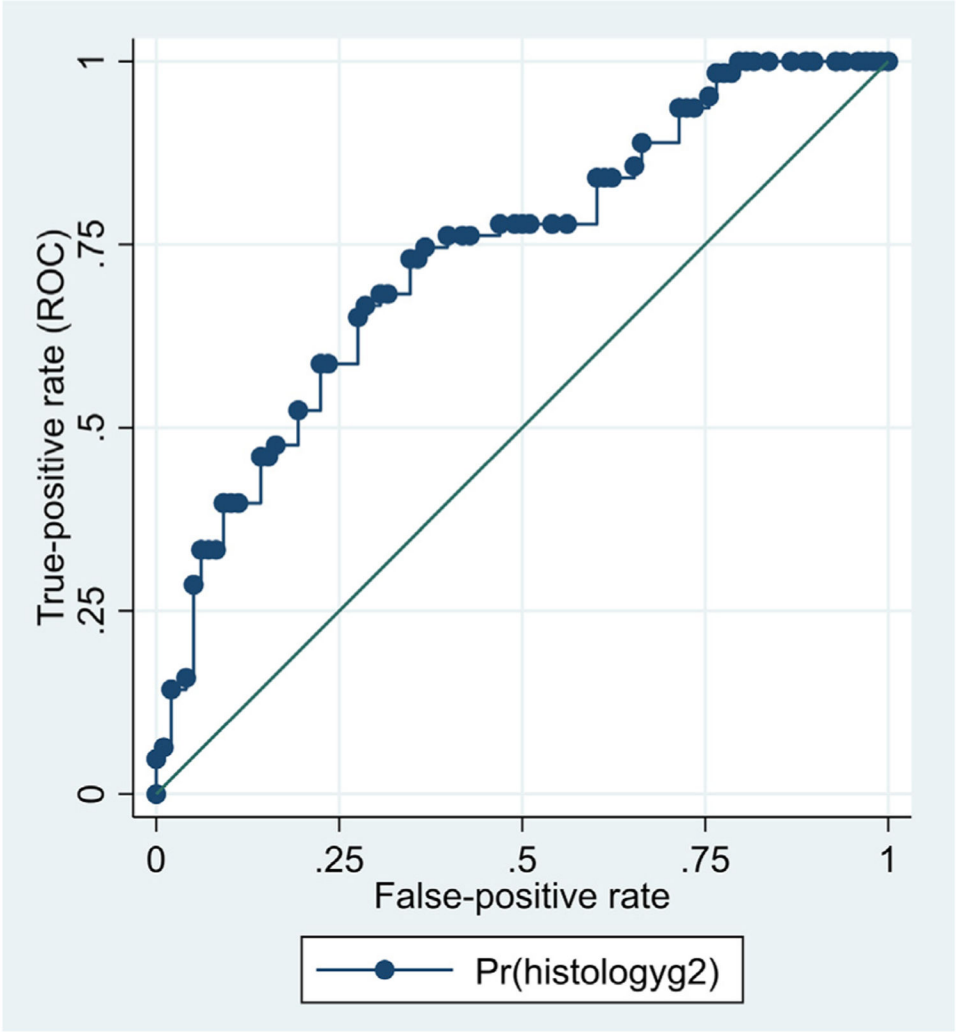

Fig. 1: Receiver operating characteristics curves in females for the model predicting anal HSIL through the complete-case analysis (n = 161) and bootstrapping (1000 replications).

The AUC estimated was 0.732 (95% CI: 0.654–0.809).

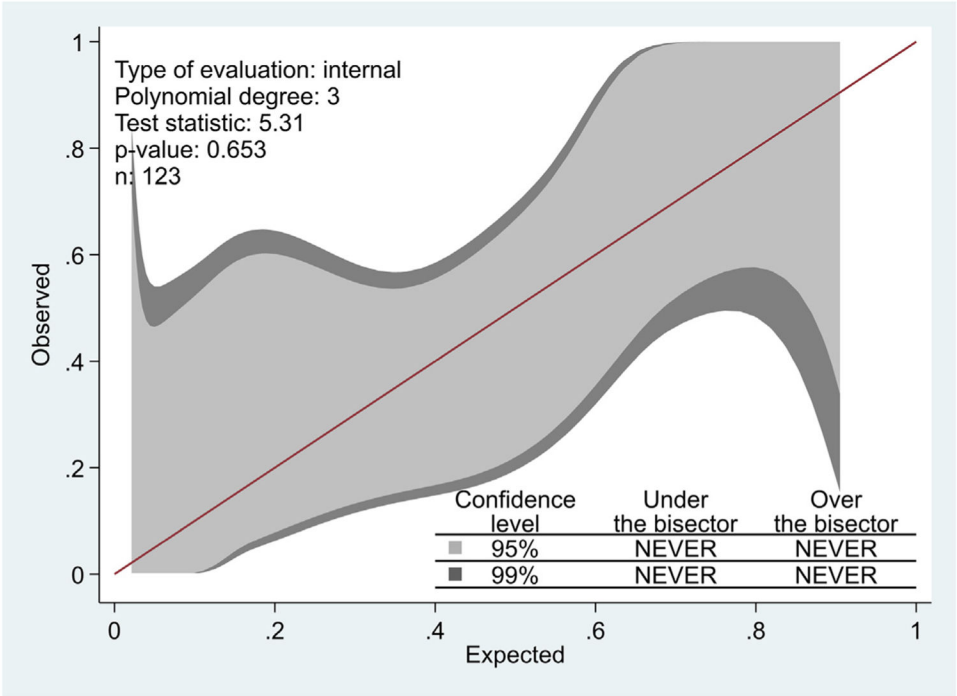

Fig. 2: Graph showing observed values of anal HSIL versus predicted values by the regression model among females.

The p-value of the Calibration belt and test for internal validation indicates no statistical difference (p = 0.653) between model predictions and the 45-grade line (perfect calibration).

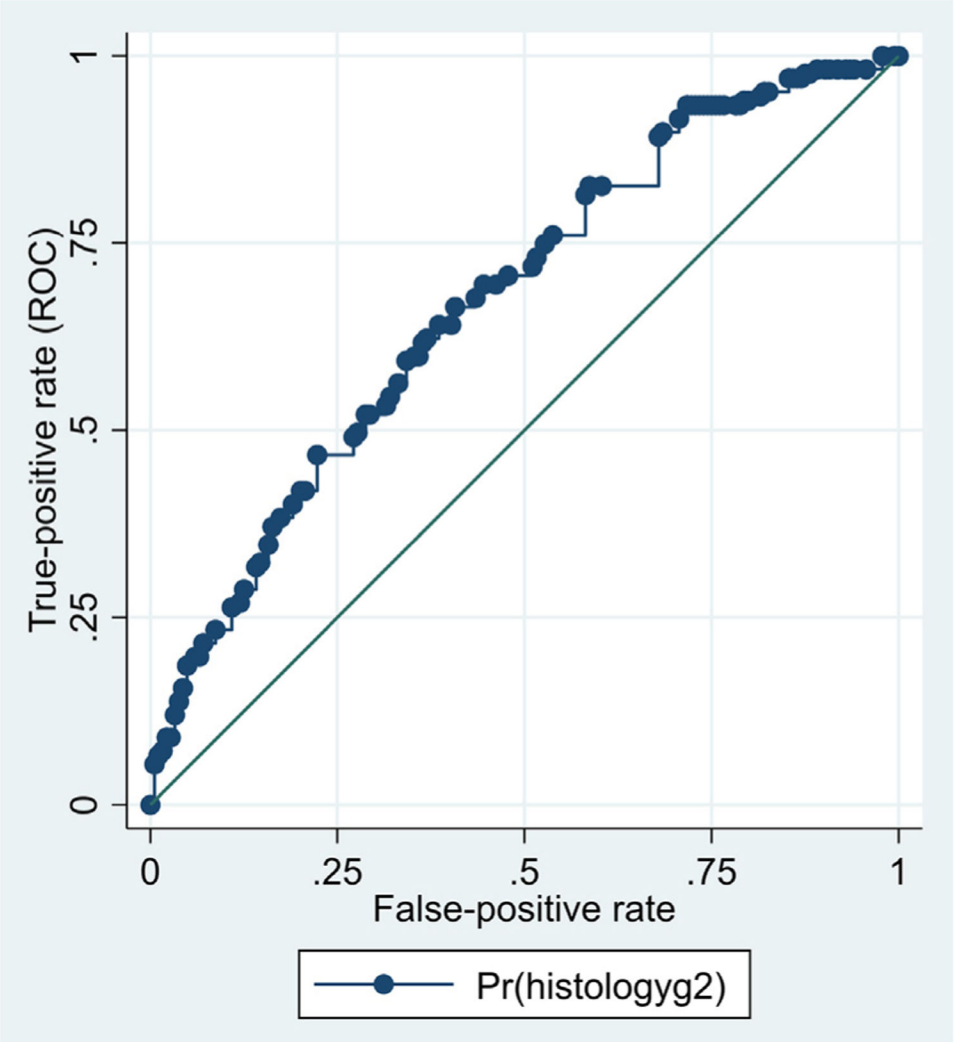

Fig. 3: Receiver operating characteristics curves in males for the model predicting anal HSIL through the complete-case analysis (n = 351) and bootstrapping (1000 replications).
The AUC estimated was 0.689 (95% CI: 0.629–0.748).

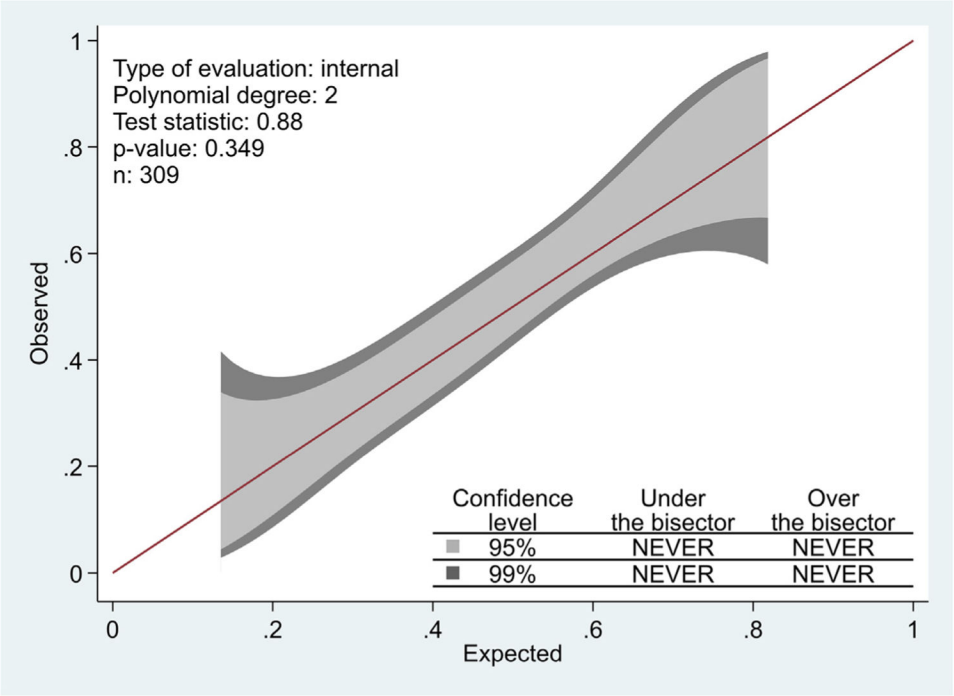

Fig. 4: Graph showing observed values of anal HSIL versus predicted values by the regression model among males.

The p-value of the Calibration belt and test for internal validation indicates no statistical difference (p = 0.349) between model predictions and the 45-grade line (perfect calibration).

Table 1:

Demographics and clinical characteristics among PLWH (n = 552) attending the Anal Neoplasia Clinic at the UPRCCC from 2016 to 2022.

Characteristics	n (%)
Anal histology	
Normal/LSIL	303 (54.89)
HSIL	249 (45.11)
Sex at birth	
Female	174 (31.52)
Male	378 (68.48)
Age at visit	
<45 y	224 (40.58)
≥45 y	328 (59.42)
Mean age ± SD	46.5 ± 12.4
Marital status	
Partnered	254 (46.01)
Single	297 (51.98)
Missing	1 (0.18)
CD4 nadir count (cells/μl)	
≥200	521 (94.38)
<200	31 (5.62)
Viral HIV load	
Undetectable (<20 to 75 cells/yL)	399 (72.28)
Detectable (>76 cells/yL)	55 (9.96)
Missing	98 (17.75)
HPV vaccine	
Yes	39 (7.07)
No	481 (87.14)
Missing	32 (5.80)
Previous anal cytology	
Normal	106 (19.20)
Abnormal	425 (76.99)
Missing	21 (3.80)
HR-HPV infection (any type)	
No	349 (63.22)
Yes	203 (36.78)
Years living with HIV	
<5	150 (27.17)
5–9	84 (15.22)
10–14	71 (12.86)
≥15	220 (39.86)
Missing	27 (4.89)

Characteristics	n (%)
BMI (kg/m^2)	
Underweight/normal	178 (32.25)
Overweight/obese	367 (66.49)
Missing	7 (1.27)
Current smoke	
No	407 (73.73)
Yes	139 (25.18)
Missing	6 (1.09)
Lifetime number of sex partners	
1 to 5 partners	139 (25.18)
6 or more	409 (74.09)
Missing	4 (0.72)
Age at first sexual intercourse	
≥19 years	136 (24.64)
16–18 years	194 (35.14)
≤15 years	213 (38.59)
Missing	9 (1.63)
Lifetime anal sex	
Insertive	51 (9.24)
Receptive/both	401 (72.64)
Missing	100 (18.12)
Sexual risk group	
Men who have sex with women	32 (5.80)
Men who have sex with men	344 (62.32)
Women	173 (31.34)
Missing	3 (0.54)
Self-report history of infection with any gonorrhea	
No	481 (87.14)
Yes	71 (12.86)

Table 2:

Magnitude of association between anal HSIL and different predictors among women living with HIV attending the Anal Neoplasia Clinic at the UPRCCC from 2016 to 2022.

Predictors	Anal histology (n = 161)		Crude odds ratio[a] (95% CI)	Adjusted odds ratio[b] (95% CI)	Adjusted odds ratio[c] (95% CI)
	Normal/LSIL, n = 98 n (%)	HSIL, n = 63 n (%)			
Age at visit					
<45 y	26 (57.78)	19 (42.22)	1.0	1.0	1.0
≥45 y	72 (62.07)	44 (37.93)	0.84 (0.42–1.68)	0.87 (0.12–6.42)	0.77 (0.37–1.60)
Previous anal cytology					
Normal	25 (89.29)	3 (10.71)	1.0	1.0	1.0
Abnormal	73 (54.89)	60 (45.11)	**6.85 (1.97–23.79) p = 0.002**	**5.63 (1.50–21.15) p = 0.01**	**6.52 (1.77–24.03) p = 0.008**
HR-HPV infection (any type)					
No	68 (66.67)	34 (33.33)	1.0	1.0	1.0
Yes	30 (50.85)	29 (49.15)	**1.93 (1.00–3.72) p = 0.05**	3.45 (0.80–14.82)	2.00 (0.98–4.10)
BMI (kg/m^2)					
Underweight/normal	25 (67.57)	12 (32.43)	1.0	1.0	1.0
Overweight/obese	73 (58.87)	51 (41.13)	1.46 (0.67–3.16)	2.31 (0.88–6.06)	1.59 (0.67–3.78)
Current smoking					
No	76 (64.96)	41 (35.04)	1.0	1.0	1.0
Yes	22 (50.00)	22 (50.00)	**1.85 (0.92–3.74) p = 0.09**	1.91 (0.84–4.39)	1.73 (0.80–3.72)
Lifetime number of sex partners					
1 to 5 partners	58 (67.44)	28 (32.56)	1.0	1.0	1.0
6 or more	40 (53.33)	35 (46.67)	**1.81 (0.96–3.44) p = 0.07**	3.00 (0.72–12.53)	1.43 (0.71–2.86)
Age at first sexual intercourse					
≥19 years	34 (72.34)	13 (27.66)	1.0	1.0	1.0
16–18 years	24 (54.55)	20 (45.45)	**2.18 (0.91–5.21) p = 0.008**	0.58 (0.09–3.82)	2.11 (0.84–5.35)
≤15 years	40 (57.14)	30 (42.86)	**1.96 (0.89–4.34) p = 0.10**	1.49 (0.24–9.02)	1.52 (0.63–3.64)

The percentage is by column.

[a]Crude Odds Ratio from the complete-case analysis (n = 161).

[b] Adjusted Odds Ratio from the complete-case analysis (n = 161) including interactions terms between age at visit with HR-HPV, lifetime number of sexual partners, and age at first sexual intercourse. Significant interaction terms were found in the MLRM ($p < 0.05$).

[c] Adjusted Odds Ratio from imputation analysis (number of observations = 174 and imputations = 10).

Table 3:

Magnitude of association between anal HSIL and different predictors among males living with HIV attending the Anal Neoplasia Clinic at the UPRCCC from 2016 to 2022.

Predictors	Anal histology (n = 351)		Crude Odds Ratio[a] (95% CI)	Adjusted Odds Ratio[b] (95% CI)	Adjusted Odds Ratio[c] (95% CI)
	Normal/LSIL, n = 184 n (%)	HSIL, n = 167 n (%)			
Age at visit					
<45 y	83 (51.55)	78 (48.45)	1.0	1.0	1.0
≥45 y	101 (53.16)	89 (46.84)	0.94 (0.62–1.43)	1.25 (0.78–2.02)	1.34 (0.85–2.11)
Previous anal cytology					
Normal	56 (73.68)	20 (26.35)	1.0	1.0	1.0
Abnormal	128 (46.55)	147 (53.45)	**3.21 (1.83–5.65) p < 0.0001**	**3.78 (2.08–6.88) p < 0.0001**	**3.33 (1.85–6.01) p < 0.0001**
HR-HPV infection (any type)					
No	153 (71.50)	110 (59.78)	1.0	1.0	1.0
Yes	61 (28.50)	74 (40.22)	**1.39 (0.90–2.14) p = 0.14**	1.34 (0.84–2.16)	1.46 (0.95–2.23)
BMI (kg/m^2)					
Underweight/normal	60 (46.51)	69 (53.49)	1.0	1.0	1.0
Overweight/obese	124 (55.86)	98 (44.14)	**0.69 (0.44–1.06) p = 0.09**	0.73 (0.45–1.17)	0.68 (0.43–1.08)
Current smoking					
No	143 (53.56)	124 (46.44)	1.0	1.0	1.0
Yes	41 (48.81)	43 (51.19)	1.21 (0.74–1.98)	1.01 (0.59–1.72)	1.08 (0.65–1.82)
Lifetime number of sex partners					
1 to 5 partners	23 (51.11)	22 (48.89)	1.0	1.0	1.0
6 or more	161 (52.61)	145 (47.39)	0.94 (0.50–1.76)	0.75 (0.38–1.48)	0.86 (0.45–1.64)
Age at first sexual intercourse					
≥19 years	49 (56.98)	37 (43.02)	1.0	1.0	1.0
16–18 years	63 (47.01)	71 (52.99)	**1.49 (0.87–2.57) p = 0.15**	1.56 (0.87–2.80)	1.39 (0.78–2.46)
≤15 years	72 (54.96)	59 (45.04)	1.09 (0.63–1.88)	1.05 (0.58–1.87)	1.07 (0.61–1.90)
Self-report history of infection with any gonorrhea					
No	164 (55.97)	129 (44.03)	1.0	1.0	1.0
Yes	20 (34.48)	38 (65.52)	**2.42 (1.34–4.35) p = 0.003**	**2.79 (1.48–5.25) p = 0.002**	**2.92 (1.60–5.35) p = 0.001**

The percentage is by column.

[a] Crude Odds Ratio from the complete-case analysis (n = 351).

[b] Adjusted Odds Ratios from the complete-case analysis (n = 351). No significant interaction terms were found in the MLRM ($p > 0.05$).

[c] Adjusted Odds Ratios from imputation analysis (number of observations = 378 and number of imputations = 10).

Table 4:

Performance of the risk prediction model[a] for anal HSIL among women living with HIV at different quintiles (AUC = 0.732, 95% normal approximation CI: 0.651–0.811).

Probability of having anal HSIL	Sensitivity	Specificity	LR+	LR−	# of referrals (%)
>0	100%	0%	1.00		161 (100.00%)
>0.21	88.89%	33.67%	1.34	0.33	121 (75.16%)
>0.22	77.78%	53.06%	1.65	0.42	95 (59.01%)
>0.34	58.73%	76.53%	2.50	0.54	60 (37.27%)
>0.58	33.33%	97.84%	4.08	0.73	29 (18.0%)

[a]Using a multivariable logistic regression model for HSIL with predictors and interaction terms (complete-case analysis, n = 161). AUC: Area under the ROC curve; ROC area: (Sensitivity + Specificity/2); LR: Likelihood ratios; Optimal cut-point selected by the Youden Statistics was 3.5.

Table 5:

Performance of the risk prediction model[a] for anal HSIL among men living with HIV at different quintiles (AUC = 0.689, 95% normal approximation CI: 0.629–0.748).

Probability of having anal HSIL	Sensitivity	Specificity	LR+	LR−	# of referrals (%)
>0	100%	0%	1.00		351 (100.00%)
>0.14	89.82%	31.52%	1.31	0.32	276 (78.63%)
>0.37	70.66%	52.17%	1.48	0.56	206 (58.69%)
>0.44	52.10%	71.20%	1.81	0.67	140 (39.89%)
>0.52	28.14%	87.50%	2.25	0.82	70 (20.00%)

[a]Using a multivariable logistic regression model for HSIL with predictors (complete-case analysis, n = 351); AUC: Area under the ROC curve; ROC area: (Sensitivity + Specificity/2); LR: Likelihood ratios; Optimal cut-point selected by the Youden Statistics was 3.5.